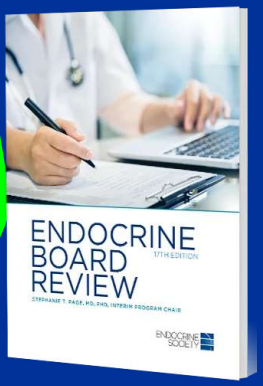
مراجعات البورد في الغدد

EBR.17



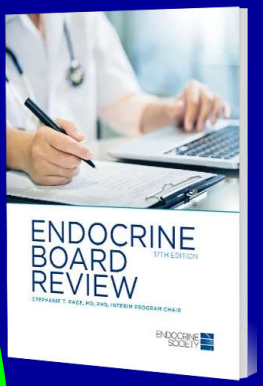
الدكتور محمد الشعباني

مراجعات البورد في الغدد

EBR.17

Pituitary

Pituitary



الدكتور محمد الشعباني

1.1. A 56-year-old ♂ presents with worsening headaches, progressive fatigue, and mild visual disturbances over the past 3 months. He notes a recent increase in thirst and urination.

Exam: bitemporal hemianopia on formal visual field testing. MRI of the sellar region shows a 2.6-cm suprasellar mass with a lobulated cystic and solid component extending toward the optic chiasm. No calcifications are seen. Imaging characteristics suggest a suspected papillary craniopharyngioma rather than an adamantinomatous subtype.

Lab: mild hyperprolactinemia, low-normal cortisol, and low-normal thyroid hormone levels. Which is the most appropriate next step in the management of this tumor?

A. Biopsy to confirm papillary craniopharyngioma and initiation of BRAF/MEK inhibitor therapy
B. Empiric dopamine agonist therapy
C. Fractionated radiation therapy to the sellar region
D. Immediate complete surgical resection of the mass
E. Stereotactic radiosurgery without further tissue diagnosis

1.2. ANSWER: A) Biopsy to confirm papillary craniopharyngioma via biopsy and initiation of BRAF/MEK inhibitor therapy: The treatment of craniopharyngiomas has shifted to a personalized approach based on tumor subtype. Surgery was traditionally the main treatment, but now different strategies are needed for adamantinomatous and papillary craniopharyngiomas due to their distinct molecular profiles. Adamantinomatous craniopharyngiomas, linked to CTNNB1 pathogenic variants, are hard to fully remove due to invasive growth, so subtotal resection followed by radiotherapy is preferred. Papillary craniopharyngiomas often have the BRAF V600E variant, making them responsive to BRAF and MEK inhibitors, which can shrink tumors significantly and set the stage for less-invasive surgeries. Papillary craniopharyngiomas often have activating BRAF pathogenic variants Evidence supports confirming the diagnosis with histopathology and then starting BRAF/MEK inhibitor therapy (Answer A).

1.3. ANSWER: A) Biopsy to confirm papillary craniopharyngioma via biopsy and initiation of BRAF/MEK inhibitor therapy:

This can shrink the tumor, ease symptoms such as headaches and visual impairment, and make surgery or radiotherapy safer and less invasive. Aggressive surgery (Answer D) or radiosurgery (Answer E) without tissue diagnosis may cause unnecessary morbidity or be ineffective if the lesion is highly responsive to targeted therapy. Radiation alone (Answer C) is not first-line treatment for a suspected papillary craniopharyngioma that may potentially have a significant response to targeted agents. Dopamine agonists (e.g., cabergoline) (Answer B) treat prolactinomas and hyperprolactinemia, not craniopharyngiomas, and the emphasis should be on tumor treatment rather than treatment of hyperprolactinemia.

Educational Objective:

Select proper management and treatment of craniopharyngiomas.

2.1. A 53-year-old ♀ with a 5-year history of acromegaly has been on pegvisomant for 4 months. She electively transitioned from somatostatin receptor ligand therapy after 3 years.
Her most recent IGF-1 measurement is well within normal limits, and her acral enlargement symptoms have markedly improved. Over the last 2 months, she has experienced mild right upper quadrant discomfort, sporadic nausea, and low-grade fatigue. She initially attributed these symptoms to a change in her work schedule.
Lab: ALT and AST levels are both about twice the upper normal limit, whereas her bilirubin and ALP remain normal. A comprehensive metabolic panel shows no other abnormalities
Abdominal US demonstrates no evidence of cholelithiasis, hepatic steatosis, or structural liver lesions. Findings on pituitary MRI are stable compared with prior studies, with no new findings. She has no history of viral hepatitis or alcohol overuse. She is concerned that pegvisomant might be harming her liver. However, her acromegaly-related symptoms are well controlled for the first time in years, and she is reluctant to switch treatments unless absolutely necessary. Which is the best next step in this patient's management?

A. Begin ursodeoxycholic acid for presumed cholestatic liver disease
B. Continue pegvisomant at the same dosage and arrange periodic liver function monitoring
C. Decrease pegvisomant dosage by 50% and add a somatostatin receptor ligand
D. Hold pegvisomant therapy for 2 weeks and recheck liver enzymes
E. Perform hepatobiliary iminodiacetic acid scan because of past somatostatin receptor ligand use.

2.2. ANSWER: B) Continue pegvisomant at the same dosage and arrange periodic liver function monitoring

Pegvisomant can cause mild elevations in liver enzymes. Current guidelines suggest that if transaminases are elevated to less than 3 times the upper normal limit and the patient has no signs of severe hepatic injury, it is generally safe to continue pegvisomant while closely monitoring liver function (Answer B). Regularly monitoring liver function (e.g., monthly or every few weeks) would determine whether her liver enzyme elevations progress. Since her IGF-1 concentration is at goal and her acromegaly-related symptoms are controlled for the first time in years, stopping or significantly reducing the pegvisomant dosage could lead to a loss of disease control. Temporarily stopping pegvisomant (Answer D) unnecessarily risks losing tight acromegaly control. A short hold might be considered if her liver enzyme concentrations rise.

2.3. ANSWER: B) Above 3 times the upper normal limit or if she develops significant hepatic symptoms. Reducing the pegvisomant dosage (Answer C) when IGF-1 levels are at target may compromise symptom control, and adding another agent (e.g., octreotide) is not indicated unless her liver enzyme concentrations increase or her clinical status worsens. There is no radiographic or laboratory evidence (e.g., markedly high liver enzymes or suspicious imaging findings) of gallstones or gallbladder sludge, which can be a consequence of long-term somatostatin receptor ligand use. Further imaging with a hepatobiliary iminodiacetic acid scan (Answer E) would not be helpful in this situation. Ursodeoxycholic acid (Answer A) is used mainly for cholestatic liver disease or gallstone-related issues. Ultrasonography shows no biliary pathology, and her primary problem is mild transaminase elevation, not cholestasis.

Educational Objective: Management of mild liver enzyme elevations in patients treated with pegvisomant for acromegaly.

3.1. A 28-year-old ♀, adopted at birth with unknown family history, presents with a 3-month history of weight loss, tremors, palpitations, and heat intolerance. She has had no changes in vision but reports occasional mild headaches.

Exam: BP: 134/78. Pulse: 96. She has a mild goiter without Ophthalmopathy. She mentions taking a low-dose over-the-counter supplement containing biotin for hair and nail health.

Lab: FT4: 2.6 ng/dL (0.8-1.8). Total T3: 320 ng/dL (70-200). TSH 1/7 mIU/L (0.5-5). A high-uptake pattern is observed on thyroid radionuclide scan. Brain MRI reveals a 0.9-cm lesion in the sellar region, without cavernous sinus invasion, consistent with a pituitary microadenoma. Which is the most appropriate next step in confirming the cause of this patient's hyperthyroidism?

A. Measure serum alpha-subunit
B. Obtain thyroid-stimulating immunoglobulin antibodies
C. Order genetic testing to search for a pathogenic variant in the thyroid hormone receptor gene
D. Repeat all thyroid function tests after discontinuing biotin for 72 hours
E. Test for heterophile antibodies

3.2. ANSWER: A) Measure serum a-subunit level

Inappropriately normal or high TSH in the presence of elevated thyroid hormones (T, and T_4), along with a pituitary adenoma on imaging, raises strong suspicion for a TSH-secreting pituitary adenoma. Most (up to 85%) of these tumors secrete high levels of the a-subunit of glycoprotein hormones (TSH, LH, FSH), making an elevated a-subunit or an Elevated a-subunit-to-TSH molar ratio diagnosis. Thus, the best next step in this patient's care is to measure serum a-subunit (Answer A). Confirming elevated a-subunit supports the diagnosis of a TSH-secreting adenoma and justifies moving toward pituitary-directed therapy. Thyroid hormone resistance could present with elevated T/T and unsuppressed TSH, but imaging evidence of a pituitary microadenoma plus a high-uptake thyroid scan more strongly favors a TSH-secreting adenoma.

3.3. ANSWER: A) Measure serum a-subunit level

Thus, genetic testing (Answer C) is incorrect. Thyroid hormone resistance is often associated with a family history of the condition (although this patient is adopted and her family history is unknown). The imaging and laboratory findings point more toward an adenoma

Although biotin can interfere with certain immunoassays, leading to erroneous thyroid function results, the presence of a sellar lesion consistent with a microadenoma—plus significant hyperthyroidism and normal/high TSH—makes a spurious (biotin-induced) laboratory abnormality far less likely. Thus, there is no need to discontinue biotin and repeat thyroid function testing (Answer D).

3.4. ANSWER: A) Measure serum a-subunit level

Heterophile antibodies (Answer E) can artifactually increase measured TSH. However, they cannot explain the pituitary lesion and the hyperthyroid symptoms with high-uptake scans.

Thyroid-stimulating immunoglobulin testing (Answer B) is used to diagnose Graves disease, but the MRI finding of a pituitary adenoma and inappropriately normal TSH is incompatible with typical Graves pathophysiology.

Educational Objective:

Guide the evaluation to confirm the diagnosis of a suspected TSH-secreting tumor

4.1. A 35-year-old ♀ presents with a 6-month history of excessive thirst and frequent urination. She reports drinking about 6 liters of water daily and experiencing nocturia 3 to 4 times per night. She has no fever, dry mouth, or recent weight loss. She has no relevant medical history and takes no medications.

Exam: BMI 22. Normal vitals. No abnormalities are observed.

Lab: Na: 142 mEq/L (136-142). Plasma osmolality: 292 mOsm/kg (275-295). Urine osmolality: 120 mOsm/kg (150-1150). To evaluate her symptoms, a water-deprivation test is performed. After 8 hours of water restriction, her plasma Na: rises to 150 mEq/L with a urine osmolality of 150 mOsm/kg. Desmopressin is administered. Unfortunately, the laboratory is unable to provide results after the desmopressin due to a lab error. The patient does not want to repeat the water-deprivation test. She receives a hypertonic saline infusion to stimulate copeptin release. Plasma Na rises to 150 mEq/L (150 mmol/L) during the test, and the plasma copeptin concentration is 1.5 pmol/L. Based on the hypertonic saline-stimulated copeptin value, which of the following conditions is most likely?

A. Arginine vasopressin deficiency
B. Arginine vasopressin resistance
C. Partial arginine vasopressin deficiency
D. Primary polydipsia
E. Syndrome of inappropriate antidiuresis

4.2. ANSWER: A) Arginine vasopressin deficiency level

Copeptin, a stable fragment of proarginine vasopressin (proAVP), is a reliable marker for arginine vasopressin (AVP), which is difficult to measure directly due to its instability and low plasma levels. Copeptin mirrors AVP secretion, making it useful in diagnosing water balance disorders, such as AVP deficiency and resistance. The patient's copeptin level during hypertonic saline infusion is 1.5 pmol/L, which is below the diagnostic threshold for primary polydipsia (>4.9 pmol/L) and is consistent with AVP deficiency (Answer A), in which copeptin levels are typically low due to deficient secretion of AVP.

In primary polydipsia (Answer D), copeptin levels increase appropriately (>4.9 pmol/L) during hypertonic saline infusion, reflecting intact AVP secretion. This patient's copeptin level is too low for this diagnosis.

4.3. ANSWER: A) Arginine vasopressin deficiency level

In AVP resistance (Answer B), copeptin levels may be normal or elevated during hypertonic saline infusion due to intact AVP secretion. Partial AVP deficiency (Answer C) would be associated with an intermediate copeptin value and a modest response to desmopressin. Syndrome of inappropriate antidiuresis (SIAD) (Answer E) typically presents with hyponatremia, not the normal or elevated sodium value seen in this patient. Additionally, copeptin levels in SIAD are inappropriately high for the plasma osmolality.

Educational Objective:

Explain the diagnostic role of copeptin during hypertonic saline infusion in distinguishing between primary polydipsia and arginine vasopressin deficiency.

5.1. A 45-year-old ♂ is referred for evaluation of a 12-mm pituitary lesion discovered incidentally during an MRI performed for chronic headaches. He has no visual disturbances, polyuria, polydipsia, fatigue, or other symptoms of pituitary dysfunction. His medical history is unremarkable, and he takes no medications.

Exam: no abnormalities, and he has normal visual fields on confrontation testing.

Lab: Na: 140 mEq/L (135-145). K: 4.3 mEq/L (3.5-5). Glucose: 92 mg/dL. He is asymptomatic, and there are no physical examination findings suggestive of hormonal hypersecretion or deficiency.

Which sets of lab investigations is most appropriate to evaluate this patient's pituitary function?

A. Morning cortisol, ACTH, and dexamethasone-suppression test
B. Serum prolactin and IGF-1
C. Serum prolactin, IGF-1, morning cortisol, TSH, FT4, LH, and FSH
D. TSH, FT4, morning cortisol, and serum prolactin
E. No laboratory evaluation is necessary in an asymptomatic patient

5.2. ANSWER: C) Serum prolactin, IGF-1, and FSH 47

The initial evaluation of an incidentally discovered pituitary lesion (pituitary incidentaloma) should include laboratory tests to assess for hormonal hypersecretion or hypopituitarism, even in asymptomatic patients. The recommended screening tests are:

1. Serum prolactin: Hyperprolactinemia is the most common finding in individuals with pituitary adenomas, including microadenomas
2. IGF-1: To screen for acromegaly caused by excess GH secretion
3. Morning cortisol: To screen for central adrenal insufficiency
4. TSH and free T_1: To assess for possible central hypothyroidism
5. Gonadotropins (LH, FSH) and sex hormones (testosterone in men, estradiol in women): To evaluate gonadal function; in a premenopausal-aged woman, menstrual history may be sufficient.

5.3. ANSWER: C) Serum prolactin, IGF-1, and FSH 47

Measuring only TSH, FT4, morning cortisol, and prolactin (Answer D) would miss possible acromegaly and hypogonadism. While measuring only prolactin and IGF1 (Answer B) is an efficient testing strategy in asymptomatic patients, this would not assess for pituitary insufficiencies that may be unnoticed by the patient and difficult to detect, even with a thorough history.

Morning cortisol, ACTH, and a dexamethasone-suppression test (Answer A) focuses on possible ACTH hypersecretion, but this is less helpful in asymptomatic patients and does not include other important tests for more common hormone hypersecretion and deficiency. There is a possibility that this patient has subclinical hormone excess or deficiency, and laboratory evaluation is critical to exclude these conditions (thus, Answer E is incorrect).

Educational Objective: Guide the appropriate laboratory evaluation of a pituitary incidentaloma, including tests for hormonal hypersecretion and hypopituitarism.

6.1. An 18-year-old boy is referred for evaluation of delayed puberty and short stature. He reports being healthy overall with no history of significant illnesses, hospitalizations, or medication use. He has not experienced voice deepening, spontaneous erections, or any significant increase in muscle mass. He feels self-conscious because his classmates have progressed through puberty, and he is shorter than most of his peers. He has no headaches, vision changes, or neurological symptoms. He has a normal sense of smell. He participates in recreational soccer but has noticed his stamina and strength lag behind that of others on his team. His family history is notable for his father recalling that he "started growing late" and reached full height in his 20s. There is no family history of infertility, pituitary tumors, or genetic disorders. His mother's height is 160 cm, and his father's height 178 cm.

Exam: height 154 cm (10th percentile) and weight 48 kg (15th percentile) (BMI: 20.2). Pubic hair is Tanner stage 2, and testicular volume is 6 mL bilaterally. He has no gynecomastia or axillary hair. The thyroid gland is normal size, and there is no goiter. Findings on visual field testing and neurologic examination are normal.

Lab: LH 1 mIU/mL (1-9). FSH 0.8 mIU/mL (1-13). Total testosterone: 80 ng/dL (300-900). Estradiol < 10 pg/ml (10-40). Inhibin B 18 pg/mL (15-300). Findings on MRI of the brain and hypothalamic-pituitary region are normal. Semen analysis demonstrates no sperm on automated analysis, but immature sperm are present with manual microscopic examination.

Which of the following best explains this patient's findings?

A. Decreased androgen receptor sensitivity in hypothalamic-pituitary feedback loops
B. Decreased kisspeptin secretion from the hypothalamus
C. Defective inhibin production by Sertoli cells
D. FSH hypersecretion due to GnRH pulsatility abnormalities
E. Increased sensitivity of GnRH neurons to negative feedback

6.2. ANSWER: B) Decreased kisspeptin secretion from the hypothalamus

Kisspeptin is a hypothalamic neuropeptide critical for the activation of gonadotropin-releasing hormone (GnRH) neurons, which initiate and regulate the pulsatile secretion of GnRH. A defect in kisspeptin secretion leads to insufficient GnRH release, resulting in low gonadotropin (LH, FSH) levels and delayed activation of the hypothalamic-pituitary-gonadal axis. The combination of low LH and FSH, low testosterone, normal findings on pituitary imaging, and poor testicular development is consistent with hypogonadotropic hypogonadism, likely due to hypothalamic dysfunction involving kisspeptin (Answer B).

Defective inhibin production by Sertoli cells (Answer C) would result in elevated FSH levels.

6.3. ANSWER: B) Because inhibin B, produced by Sertoli cells in response to FSH, provides negative feedback to selectively suppress FSH secretion. In this case, the patient's FSH levels are low, making defective inhibin production an unlikely cause.

Increased sensitivity of GnRH neurons to negative feedback (Answer C) could suppress gonadotropin secretion, but this mechanism is typically seen in conditions such as functional hypogonadotropic hypogonadism related to excessive exercise, stress, or significant weight loss—none of which is present in this patient.

FSH hypersecretion due to GnRH pulsatility abnormalities (Answer D) is also unlikely, as such abnormalities might cause dysregulation of gonadotropin levels, but FSH hypersecretion would be inconsistent with the low gonadotropin levels observed here.

6.4. ANSWER: B)

Lastly, decreased androgen receptor sensitivity in the hypothalamic-pituitary feedback loop (Answer A) would result in inadequate negative feedback, leading to low LH and FSH levels. However, this patient exhibits low levels of these hormones, which rules out androgen receptor insensitivity as the cause.

Educational Objective:

Explain the role of kisspeptin and other key regulators of gonadotropins (LH, FSH) in the pathophysiology of pubertal delay and hypogonadotropic hypogonadism.

7.1. A 43-year-old ♀ with panhypopituitarism due to a nonfunctioning pituitary macroadenoma treated surgically 3 years ago presents for follow-up. For the past year, her condition has been stable on the following hormone replacement regimen: hydrocortisone, 10 mg in the morning and 5 mg in the afternoon, for central adrenal insufficiency, and Levothyroxine 100 mcg/day, for central hypothyroidism. Recently, due to persistent symptoms of fatigue, low libido, and hot flashes, she was prescribed oral estradiol, 2 mg daily, with cyclic progesterone for hypogonadotropic hypogonadism and GH replacement therapy at a dosage of 0.3 mg/day for GH deficiency. Before initiating GH therapy, her IGF1 was 85 ng/mL (98-261 ng/mL).. After 2 months of treatment, IGF1: decreased slightly to 78 ng/ml despite adherence to therapy. She now returns with concerns of worsening fatigue, cold intolerance, and weight gain, which began shortly after starting the new hormone therapies. She has no dizziness, nausea, or postural symptoms.

Lab: TSH 0.1 mIU/L (0.5-5). TT4: 13.5 µg/dL (5.5-12.5 µg/dL). FT4: 0.75 ng/dL (0.8-1.8). Morning cortisol: 6 µg/dL (5-25 µg/dL). IGF-178 ng/mL (98-261).

Exam: unremarkable, with stable BP and heart rate. Which is the most appropriate next step in this patient's management?

A. Decrease levothyroxine dosage to 88 mcg daily
B. Increase GH dosage to 0.4 mg daily
C. Increase hydrocortisone dosage to 15 mg in the morning and 5 mg in the afternoon
D. Increase levothyroxine dosage to 112 mcg daily
E. Switch from oral estrogen to a transdermal estrogen patch

7.2. ANSWER: D) Increase levothyroxine dosage mg daily

This patient's worsening fatigue, cold intolerance, and weight gain are consistent with hypothyroidism due to inadequate thyroid hormone replacement. The key finding is her slightly low free T_1 level (0.75 ng/dL [9.7 pmol/L]) despite being on stable levothyroxine therapy. Oral estrogen increases thyroxine-binding globulin levels, which binds more circulating thyroid hormone, thereby increasing total T_2 but reducing free T_2 levels. GH therapy reduces type 2 deiodinase activity, which impairs the conversion of T_2 to T_2, further contributing to hypothyroid symptoms. In central hypothyroidism, TSH is unreliable for monitoring therapy because it may appear low, normal, or even slightly elevated despite actual thyroid hormone deficiency. The elevated total T_2 is misleading due to increased thyroxine-binding globulin from estrogen therapy.

7.3. ANSWER: D) Increase levothyroxine dosage mg daily

The most accurate assessment comes from the free T_1 level Despite a high total T_1, the patient's free T, and symptoms confirm underreplacement, requiring an increase (Answer D), not a decrease (Answer A), in the levothyroxine dosage. The levothyroxine dosage should be titrated to target the mid- to upper normal free T range. The patient shows no signs of adrenal insufficiency, so increasing the hydrocortisone dosage (Answer C) is incorrect. Increasing hydrocortisone unnecessarily could cause adverse effects, such as weight gain, hypertension, and glucose intolerance.

While transdermal estrogen (Answer E) has less impact on thyroxine-binding globulin and may reduce the need for a higher levothyroxine dosage, the immediate priority is to correct the hypothyroidism by adjusting the levothyroxine dosage.

7.4. ANSWER: D) Increase levothyroxine dosage mg daily

Switching to a transdermal estrogen patch may be considered later, but it would not rapidly address her current symptoms

Although her IGF-1 level remains low, GH dosage adjustments (Answer B) should not be made in the setting of undertreated hypothyroidism, as hypothyroidism blunts the GH response.

Educational Objective:

Explain the relationships between hormone replacement and thyroid hormone concentrations in multiple pituitary deficiencies and panhypopituitarism.

8.1. A 42-year-old ♂ is found to have a 2.4–8 cm sellar mass on CT performed in the emergency department following minor head trauma. His Exam: normal.

Lab: mild prolactin elevation of 31 ng/dL. Following surgery for what is determined to be a gonadotroph adenoma, his pituitary function is normal, but the 3-month postoperative MRI clearly shows a residual tumor present in the cavernous sinus. The patient is very concerned about persistence of the tumor. Which treatments is most likely to prevent further growth of the residual adenoma?

A. GnRH antagonist
B. Pasireotide
C. Pegvisomant
D. Radiotherapy
E. Repeated surgery

8.2. ANSWER: D) Radiotherapy first-line: Treatment for clinically nonfunctioning pituitary adenomas, but tumor tissue left in the sellar area has the potential for subsequent regrowth. Although it is not recommended as a routine treatment for every case, radiotherapy (Answer D) can be used to reduce tumor mass or prevent remnant regrowth. There are no randomized controlled trials of radiotherapy versus other treatment options, but several retrospective series have shown that individuals who undergo postoperative radiotherapy for clinically nonfunctioning pituitary adenomas have a 50% lower recurrence rate than those who are simply observed when a residual tumor is seen on MRI. Although repeated surgery (Answer E) would be useful for managing residual disease, the current tumor is in the cavernous sinus and is unlikely to be accessible for resection.

Pegvisomant (Answer C) is a treatment for acromegaly, and it has no role in the management of gonadotroph adenomas Although GnRH antagonists (Answer A) make theoretical sense to try in patients with gonadotroph adenomas based on the assumption that GnRH may stimulate gonadotroph cells, in practice their use has not been shown to be beneficial. There are no data on the use of pasireotide (Answer B) for patients with nonfunctioning adenomas.

Educational Objective:

Guide the long-term management of clinically nonfunctioning pituitary adenomas.

9.1. A 32-year-old ♀ is referred by her gynecologist because of a 1.5-year history of amenorrhea and galactorrhea and a prolactin concentration of 39.3 ng/mL.

Exam: normal except for bilateral expressive galactorrhea. No clinical evidence of Cushing syndrome or acromegaly.

MRI shows a 1.4-cm pituitary adenoma with minimal suprasellar extension.

Lab: Prolactin 41.3 ng/mL (4-30). LH 2.3 mIU/mL (1-18). FSH 1.7 mIU/mL (2-12). Cortisol (8 AM) 17.3 µg/dL (5-25).

IGF-1469 ng/mL (113-297). Which is the best next step in this patient's management?

A. Measure GH during an oral glucose tolerance test
B. Refer to neurosurgery for transsphenoidal pituitary resection
C. Remeasure prolactin levels after 1:100 dilution
D. Start cabergoline, 0.5 mg twice weekly
E. Start octreotide LAR, 20 mg monthly

9.2. ANSWER: A) Measure GH during an oral glucose tolerance test: There is a discrepancy in this case between the degree of prolactin elevation and the tumor size, implying that this is not a simple prolactin-secreting macroadenoma. However, the tumor is not so large that one would assume the prolactin levels would be very high (>10,000 ng/mL [>434.8 nmol/L]) requiring a 1:100 dilution to rule out the "hook effect" (Answer C). Testing was done appropriately to rule out hypopituitarism in this patient with a macroadenoma, and her IGF-1 level was elevated—a surprising finding given that she had no clinical evidence of acromegaly. The possibility of subclinical GH hypersecretion should be evaluated further by measuring GH after hyperglycemia is induced during an oral glucose tolerance test (Answer A). There is no urgency for surgery before determining tumor type (Answer B), and medications (Answers D and E) should not be started before determining whether this is indeed a GH-secreting tumor. In fact, the patient did have a GH-secreting tumor that was surgically removed, and she remarked 3 months later how much finer her facial features appeared, how much looser her rings felt, how she had stopped snoring, how her skin seemed less oily, and how much better she felt overall.

Educational Objective: Characterize all clinically nonfunctioning tumors for subclinical hyperfunction or hypofunction.

10.1. A 37-year-old ♀ has been treated for a prolactinoma. Her prolactin concentration was initially 1593 ng/mL, and a 2.6-cm macroadenoma was visible on MRI. She responded well to cabergoline 0.5 mg twice/week, with initial normalization of her prolactin level and shrinkage of her tumor to The tumor was about 7 mm in height. However, 18 months later, her prolactin increased to 284 ng/mL. MRI: tumor grew to 1.4 cm. She reported taking her medication regularly. She had not had menstruation for several months. Her cabergoline dosage was gradually increased, initially to 1 mg twice/week and subsequently to 2 mg/day over the next year. However, her prolactin level continued to rise to 4513 ng/mL, and tumor grew to 3.2 cm. The patient adhered to her medication regimen and attended her clinic appointments. She subsequently underwent a two-stage transsphenoidal/transcranial near-total resection. However, the tumor regrowed rapidly even on cabergoline, and she underwent stereotactic radiotherapy. Over the following two years, the tumor continued to grow, and she was experiencing vision loss. Which treatments is the best choice now?

A. Conventional radiotherapy
B. Ipilimumab
C. Lanreotide
D. Repeat craniotomy
E. Temozolomide

10.2. ANSWER: E) Temozolomide: This patient has a rapidly enlarging macroprolactinoma that has been unresponsive to cabergoline, two operations, and stereotactic radiotherapy. The tumor is certainly acting in a malignant fashion. However, distant metastases would have to be demonstrated for this to qualify as true malignancy. Some of these very aggressive tumors and some true pituitary carcinomas respond to temozolomide (Answer E), an alkylating agent used primarily for the treatment of glioblastomas. However, even patients who respond to this agent for a while may, over time, have a poor outcome. Additional radiotherapy (Answer A) or surgery (Answer D) is unlikely to help. It is extremely rare for a patient with a prolactinoma to respond to a somatostatin analogue, such as lanreotide (Answer C).
Ipilimumab (Answer B) can cause hypophysitis and is a monoclonal antibody used in the treatment of some cancers.
Educational Objective: Recommend a treatment strategy for aggressive pituitary tumors and pituitary carcinomas.

11.1. A 41-year-old man presents with fatigue. His history is notable for a severe frontal throbbing headache 8 months prior that came on suddenly and lasted 4 days. He decided not to go to a hospital at that time. Since then, he has noted progressive fatigue. He has a distant history of renal cell carcinoma that was managed with total resection, and he is currently in remission. He has no polyuria or polydipsia.

Exam: he appears fatigued but comfortable. BP: 96/68. Pulse: 74. He has increased abdominal girth.

Lab: glucose 109 mg/dL. TSH: 1.2 mIU/L (0.5-5). FT4: 1.3 ng/dL (0.8-1.8). Cortisol (8 AM) 15 µg/dL (5-25). Total testosterone (8 AM) 250 ng/dL (300-900). IGF: 182 ng/mL (98-261). MRI: empty sella with irregularity of soft tissue along the left side of the sellar floor. Which is this patient's most likely diagnosis?

A. Craniopharyngioma
B. Lymphocytic hypophysitis
C. Metastasis to the sella
D. Neurosarcoidosis
E. Pituitary apoplexy

11.2. ANSWER: E) Pituitary apoplexy description of an enlarged sella turcica that is not entirely filled with pituitary tissue.

By itself, this is not a clinical condition but is a reflection of an underlying disorder. Primary empty sella is characterized by a defect in the diaphragma sellae that is thought to allow cerebrospinal fluid pressure to enlarge the sella. Hypopituitarism has been described in a subset of such patients. Secondary empty sella is characterized by the association of an empty sella with identifiable disease of the pituitary gland. In this scenario, a remnant of a partially destroyed pituitary adenoma with an empty sella suggests that the remaining pituitary gland could have residual function, although the patient is at risk for hypopituitarism. This patient's laboratory tests show mostly adequate pituitary function, but his IGF-1 concentration is low, suggesting the presence of GH deficiency (this diagnosis requires.

11.3. ANSWER: E) Pituitary apoplexy description of an enlarged sella turcica that is not entirely filled with pituitary tissue.

Confirmation by provocative testing. The progressive fatigue and increased abdominal girth could be explained by GH deficiency. One example of secondary empty sella is in the setting of apoplexy (infarction/hemorrhage) of a preexisting pituitary tumor, which may be associated with abrupt onset of headache and, depending on the extent of the apoplexy and subsequent healing of the sellar contents, hypopituitarism. By history, apoplexy into a pituitary adenoma (Answer E) is the most likely diagnosis in this patient.

Metastasis to the sella (Answer C) is unlikely given lack of clear disease on MRI and arginine vasopressin deficiency, which would be common in patients with metastasis to the sella.

11.4. ANSWER: E) Pituitary apoplexy description of an enlarged sella turcica that is not entirely filled with pituitary tissue.

There is no clinical, biochemical, or radiologic evidence to suggest craniopharyngioma (Answer A).

The presentation of lymphocytic hypophysitis (Answer B) is usually one of contrast-enhancing, homogeneous enlargement of the sella associated with adrenal insufficiency and arginine vasopressin deficiency.

Similarly, neurosarcoidosis (Answer D) usually presents with arginine vasopressin deficiency, and it is unusual for affected patients to have acute-onset headaches along with empty sella.

Educational Objective:

Determine the most likely etiology of empty sella.

12.1. A 29-year-old ♂ is referred because a head CT scan performed in the emergency department after an automobile crash showed an empty sella. Subsequent MRI shows an enlarged sella and minimal tissue along the floor of the sella, with the hypothalamic-pituitary stalk reaching the sellar floor. He was generally well before the accident. However, he states that he received GH injections for many years as a child and that he stopped receiving them when he completed growth at age 18. He has also taken thyroid hormone since age 12.
Which is the most likely cause of this patient's empty sella?

A. Hemochromatosis
B. Langerhans cell histiocytosis
C. Pituitary sarcoidosis
D. PROPI pathogenic variant
E. Trauma-induced pituitary infarction

12.2. ANSWER: D) PROPI pathogenic variant

Pathogenic variants in the genes encoding several transcription factors, including POUIFI (formerly PITI) and PROPI, can cause disruption in the development of many pituitary cell types during embryogenesis, resulting in multiple pituitary hormone deficiencies. Pathogenic variants in the PROPI gene (Answer D) result in a decrease in PROP 1, a transcription factor important for the development of the somatotroph, lactotroph, and thyrotroph lineages, with deficiencies in their respective hormones. Some affected individuals also have delayed puberty. Combined pituitary hormone deficiency (GH, prolactin, TSH) has an incidence of about 1 in 8,000 births, and 10% have an affected family member. Between 25% and 50% of these cases are due to POUIFI or PROPI pathogenic variants.

12.3. ANSWER: D) PROPI pathogenic variant

In this patient, the history of previous GH and thyroid hormone treatment starting in childhood suggests congenital combined pituitary hormone deficiency In some children with PROPI deficiency, there is early pituitary enlargement of uncertain cause, which results in sellar enlargement and subsequent loss of pituitary volume, leading to an empty sella. In most series, when patients with empty sellas have evaluations of pituitary function, one-quarter to one-third have varying degrees of hypopituitarism. Acute trauma causing pituitary infarction (Answer E) would show blood in the pituitary with pituitary enlargement rather than a small pituitary.

12.4. ANSWER: D) PROPI pathogenic variant

Sarcoidosis (Answer C) and Langerhans cell histiocytosis (Answer B) are infiltrative diseases of the hypothalamus and pituitary stalk and might present with stalk thickening rather than an empty sella. Both usually also present with arginine vasopressin deficiency.

Hemochromatosis (Answer A) can cause iron deposition in the pituitary and usually affects the gonadotroph cells; it is not associated with an empty sella.

Educational Objective:

Construct the differential diagnosis of an empty sella.

13.1. A 35-year-old ♂ with a history of 13 episodes of hypopituitarism after surgery Removal of a nonfunctioning pituitary tumor is of interest to the patient regarding fertility. He has a 7-year-old son. A 1.7-cm, nonsecretory pituitary macroadenoma was detected incidentally at age 32, and he underwent transsphenoidal surgery. He has panhypopituitarism and is currently taking hormones Replacement with levothyroxine, hydrocortisone, GH, and intramuscular testosterone ester. He discontinued testosterone injections 3 months ago. He feels well and states he has normal libido and erectile function.

Exam: he is well virilized. Testes are 8 cc bilaterally and have normal consistency. Two semen analyses have documented azoospermia.

Lab: Testosterone 78 ng/dL (300-900). LH 0.9 mIU/mL (1-9). FSH: 1.1 mIU/ml (1-13).

Which is the best next step in this patient's management?

A. Refer for microdissection testicular sperm extraction
B. Start clomiphene citrate
C. Start hCG injections, 3 times weekly
D. Start hCG injections, 3 times weekly, and FSH injections, twice weekly
E. Suggest he consider adoption

13.2. ANSWER: C) Start hCG injections, 3 times weekly

This man has infertility based on azoospermia on semen analysis. In his case, infertility is most likely the result of hypogonadotropic hypogonadism. He had pre-existing fertility, as he fathered a child before diagnosis and treatment of his pituitary tumor. The goal now is to reestablish fertility through gonadotropin therapy. In up to 90% of men with hypogonadotropic hypogonadism, gonadotropin treatment results in the appearance of sperm in the ejaculate, although the achieved sperm are often not normal. Even if pregnancy does not occur spontaneously, the number of sperm is often sufficient for pregnancy to be achieved by insemination with the patient's semen (intrauterine insemination) or with the help of assisted reproductive technology, such as in vitro fertilization with or without intracytoplasmic sperm injection.

13.3. ANSWER: C) Start hCG injections, 3 times weekly

LH, through its substitute hormone hCG, is always replaced first before FSH because hCG alone may be sufficient for Stimulation of spermatogenesis (thus, Answer C is correct and Answer D is incorrect). Men treated with both hCG and hMG (human menopausal gonadotropin) achieve sperm production in approximately 6 to 10 months, but the time to pregnancy is longer. In this patient with secondary hypogonadism, a blockage in his duct system is unlikely and thus testicular sperm extraction (Answer A) would not be a technique used initially Because clomiphene citrate (Answer B) requires an intact pituitary gland for efficacy, this medication would not be useful in the setting of hypopituitarism. The chances for fertility in a patient such as this are well over 50%, and suggesting adoption at this point (Answer E) would be premature.

Educational Objective: Manage infertility in men with hypopituitarism.

14.1. A 37-year-old ♀ is found to have a prolactin 1012 ng/mL when evaluated for amenorrhea and galactorrhea. She also has headaches and decreased energy.

Lab: FT4: 0.6 ng/mL (0.8-1.8). TSH 0.62 mIU/L (0.5-5). Cortisol: 4.7 µg/dL (5-25). LH 2.1 mIU/mL (1-18). FSH 2.9 mIU/mL (2-12). IGF: 1142 ng/mL (160-360). MRI: 2.5-cm macroadenoma that extends laterally into the cavernous sinus on the left side and inferiorly into the sphenoid sinus. After replacement with hydrocortisone and levothyroxine, cabergoline is initiated and the dosage is gradually increased to 1 mg twice weekly. Over the next 3 months, her prolactin level normalizes, menstruation resumes, energy improves, and headaches resolve. However, over the past 2 weeks, she has noticed profuse, watery rhinorrhea. Which is the best next step in this patient's management?

A. Add pseudoephedrine
B. Increase the cabergoline dosage
C. Measure β2-transferrin in the nasal discharge
D. Perform pituitary MRI
E. Reduce the cabergoline dosage

14.2. ANSWER: C) Measure β2-transferrin in the nasal discharge

Cerebrospinal fluid rhinorrhea can occur when there is a large, invasive, skull-based prolactinoma that serves as a "cork" in the base of the skull

When the tumor size is substantially reduced through dopamine agonist use, cerebrospinal fluid can leak around the tumor into the sphenoid sinus and nasal passages. The development of profuse rhinorrhea in this patient suggests that this is what is happening. To differentiate between cerebrospinal fluid and simple nasal mucus, the fluid should be sent to the laboratory to measure β2-transferrin (Answer C), which is an asialotransferrin isoform found only in cerebrospinal fluid, ocular fluids, and perilymph. β2-Transferrin is an accepted marker of cerebrospinal fluid leakage. The major concern with such leaks is the risk of meningitis, and surgical repair is needed.

14.3. ANSWER: C) Measure β2-transferrin in the nasal discharge

Although reducing the cabergoline dosage (Answer E) may cause the tumor size to increase, thus plugging the leak, judging the exact dosage and the change in tumor size is difficult and not reliable.
Increasing the cabergoline dosage (Answer B) would not help.
MRI (Answer D) would only show that the tumor is smaller, but it would not demonstrate the leak.
Pseudoephedrine (Answer A) may decrease nasal congestion, but it would not affect cerebrospinal fluid leakage.

Educational Objective:

Manage potential complications of dopamine agonist use in patients with prolactin-secreting macroadenomas.

15.1. A 45-year-old ♀ is referred after a 2.2 x 1.8-cm, hypodense right adrenal nodule is found during a staging CT scan for recently diagnosed breast cancer. She is asymptomatic and has no clinical signs of Cushing syndrome.

Lab: DHEA-S, normal. Androstenedione: normal. Testosterone: normal. Urinary metanephrine: normal. Urinary free cortisol: normal. Cortisol (AM) 13.1 µg/Dl. (fails to suppress with dexamethasone). With a diagnosis of an incidental adenoma causing subclinical Cushing syndrome rather than an adrenal metastasis, she undergoes surgery and irradiation for breast cancer. Four months after completion of these treatments, she reports some facial rounding and erythema, peripheral edema, and worsening hirsutism.

Exam: increased hair growth and appears mildly cushingoid.

Urinary free cortisol excretion is 228 µg/24 h (629.3 nmol/d). Which of the following is the best next step in this patient's management?

A. Measure 8-AM cortisol and ACTH
B. Perform bilateral adrenal vein sampling for cortisol
C. Perform cosyntropin-stimulation testing with measurement of 17-hydroxyprogesterone
D. Perform inferior petrosal sinus sampling for ACTH
E. Refer for laparoscopic right adrenalectomy

15.2. ANSWER: A) Measure 8-AM cortisol and ACTH levels

This patient's hypercortisolism was mistakenly assumed to be due to an adrenal adenoma. About 10% of adrenal incidentalomas are bilateral. Bilateral macronodular hyperplasia can occur in patients with Cushing's disease (i.e., from excessive pituitary secretion of ACTH). In studies in which abdominal CT was performed in all patients with Cushing's disease, 5% to 17% have bilateral macronodular hyperplasia, and several cases have been reported in which there was marked asymmetry with a large nodule on one side and questionable activity on the other. In patients with Cushing's syndrome, ACTH should always be measured (Answer A). This patient's ACTH concentration was elevated, and Cushing's disease was cured by resection of a pituitary adenoma with a resulting improvement in her symptoms and hirsutism and a reduction in the size of the adrenal nodule.

15.3. ANSWER: A) Measure 8-AM cortisol and ACTH levels

Cosyntropin-stimulation testing with measurement of 17-hydroxyprogesterone (Answer C) is sometimes helpful when Diagnosing 21-hydroxylase deficiency but not Cushing syndrome. Adrenal-directed evaluations/treatment (Answers B and E) should be done only if the ACTH level is suppressed. Inferior petrosal sinus sampling for ACTH (Answer D) is done in patients in whom it is difficult to distinguish between a pituitary or an ectopic source of ACTH.

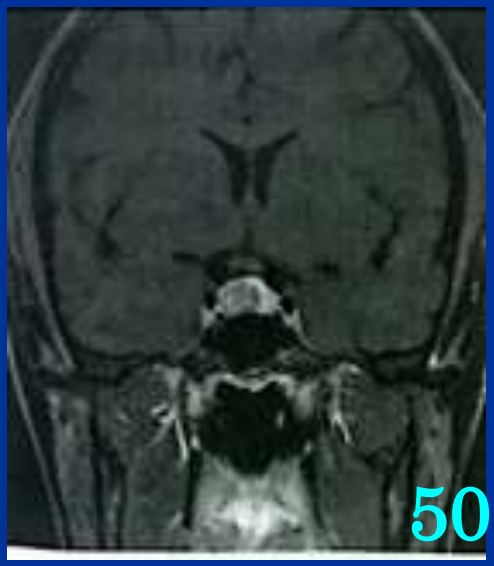
Educational Objective: Evaluate patients with Cushing syndrome.

16.1. A 48-year-old ♂ is referred after a head MRI performed for evaluation of headache showed a 0.9-cm, right-sided pituitary adenoma without parasellar extension (see image). He has been feeling well. He has no vision symptoms.

Exam: BP: 136/70. Pulse: 74. Skin: normal, reflexes: normal. He saw a local neurosurgeon who recommended surgery.

Lab: (8 AM): Testosterone: 325 ng/dL (300-900). LH: 2.3 mIU/mL (1-9). FSH: 1.4 mIU/mL (1-13). Cortisol (8 AM) 15.7 µg/dL (5-25). Prolactin 22 ng/mL (4-23). FT4: 1.2 ng/dL (0.8-1.8). Na: 143 mEq/L (136-142). IGF: 1269 ng/mL (113-297). Which is the best next step in this patient's management?

A. Another MRI in 12 months
B. Initiation of cabergoline, 0.5 mg twice weekly
C. Radiotherapy
D. Transsphenoidal surgery
E. Visual field testing



16.2. ANSWER: A) Another MRI in 12 months

This 48-year-old patient has an incidentally discovered pituitary microadenoma. Because he has no symptoms or biochemical demonstration of hormone excess or deficiency, there is no indication for surgery (Answer D) or radiotherapy (Answer C). Appropriate management would simply be to perform serial monitoring and assess for a change in tumor size in 12 months with another MRI (Answer A). Tumors such as this one grow quite slowly (0.6 mm/y on average), so he is in no imminent danger from tumor growth. If the MRI had shown significant suprasellar extension with abutment of the optic chiasm, then visual field testing (Answer E) should have been performed; otherwise, it should not. This patient does not have hyperprolactinemia, and there is no evidence to support the treatment of nonfunctional pituitary tumors with cabergoline (Answer B).

Educational Objective: Manage a pituitary incidentaloma.

17.1. Cushing's disease is diagnosed in a 33-year-old ♂. MRI shows a 4-mm pituitary lesion. Following transsphenoidal surgery, her morning cortisol 1.2 µg/dL, and she is discharged home on glucocorticoids, which are weaned over 4 months. She loses weight, and her Cushingoid appearance resolves over the next 6 months. 18 months after surgery, she returns for a clinic visit, as she is concerned about potential recurrence of Cushing's syndrome. BP 133/88. She has modest moon facies, facial plethora, and modest supraclavicular fat. She undergoes a 1-mg overnight dexamethasone-suppression test, and the morning cortisol 1.2 µg/dL (5-25) (8 AM): 35 pg/mL (10-60). FT4: 1.7 ng/dL (0.8-1.8). Which is the best test to evaluate for Cushing syndrome now?

A. Another ACTH measurement
B. Late-night salivary cortisol measurement
C. Measurement of morning serum cortisol in 6 months
D. Measurement of 24-hour urinary free cortisol excretion
E. Pituitary MRI

17.2. ANSWER: B) Late-night salivary cortisol measurement

Following transsphenoidal surgery for Cushing's disease, the recurrence rate is approximately 25% at 5 years. The degree to which cortisol decreases after surgery correlates with long-term remission. Therefore, it is important to perform serial evaluation for possible recurrence. Patients are often perceptive as to whether they have had recurrence, and this information is useful in planning testing. The most accurate test for recurrence is late-night salivary cortisol measurement (Answer B). In recent studies, late-night salivary cortisol measurement had the highest predictive value compared with overnight dexamethasone testing and 24-hour urinary free cortisol excretion (Answer D). Repeating ACTH measurement (Answer A) is not useful for determining recurrence. Once recurrence has been confirmed, pituitary MRI (Answer E) should be performed to evaluate for a visible adenoma

A plan to perform serial monitoring with serum cortisol measurement in 6 months (Answer C) is not an ideal option for this patient, as she has some signs consistent with Cushing's disease recurrence, so further testing should be performed now. In addition, an isolated serum cortisol measurement is not useful for determining recurrence

Educational Objective:

Assess patients with Cushing's disease for recurrence following successful surgery.

18.1. A 30-year-old ♀ develops progressive, severe headaches, nausea, vomiting, and fatigue during her 33rd week of pregnancy. She has no notable medical history and was able to become pregnant within 2 months of trying. Her pregnancy has been smooth so far.

Exam: normal for 33 weeks' gestation. Her obstetrician persuades the radiologist to perform a non-contrast MRI of her head, and she is found to have a diffusely enlarged pituitary gland with suprasellar extension to the optic chiasm but without compression of the chiasm.

Lab: TT4: 13 µg/dL (5.5-12.5). TSH 1.3 mIU/L (0.5-5). Cortisol (8 AM) 6 µg/dL (5-25). ACTH (8 AM) 9.3 pg/mL (10-60). Prolactin 137 ng/mL (4-30). Which is the best explanation for this mass?

A. Histiocytosis
B. Lymphocytic hypophysitis
C. Normal pregnancy
D. Prolactinoma
E. Rathke cyst

18.2. ANSWER: hypophysitis

This pregnant woman has pituitary enlargement presenting near term, and it is most likely to be lymphocytic hypophysitis (Answer B). MRI shows diffuse pituitary enlargement, which is more compatible with hypophysitis than a pituitary adenoma (Answer D). Had gadolinium been given, there would have been diffuse enhancement rather than focal enhancement. No data show adverse effects of performing MRI or giving gadolinium during pregnancy, although it is recommended to withhold gadolinium during pregnancy. One of the striking features of hypophysitis occurring during pregnancy is the high risk of ACTH deficiency, and the lab tests shown here suggest the presence of central adrenal insufficiency. Thus, glucocorticoids should be administered. Histiocytosis (Answer A) is not more common in pregnancy, and it usually presents with arginine vasopressin deficiency and a posterior sellar mass. The radiographic characteristics of the lesion are not consistent with a Rathke cyst (Answer E). Of note, enlarged pituitary contents may be seen in normal pregnancy (Answer C). However, the presence of central hypoadrenalism and headaches argues against a normal pituitary gland.

Educational Objective: Diagnose lymphocytic hypophysitis in a pregnant woman. is

19.1. A 65-year-old ♂ has a history of renal cell carcinoma with metastases to the lung. He has been undergoing chemotherapy, including treatment with nivolumab. Approximately 5 months earlier, he complained of headaches, but findings on brain MRI were normal. Over the past 3 weeks, he has noted an abrupt onset of frequent urination and increased thirst, along with new headaches. An MRI is performed, which documents a 1.5-cm, hypoenhancing sellar mass.

Exam: he appears tired. BP: 98/66. Pulse: 92. BMI: 21.

Lab: Na: 152 mEq/L (136-142). Prolactin: 53 ng/mL (4-30). Glucose: 89 mg/dL. FT4: 0.9 ng/dL (0.8-1.8). TSH: 0.8 mIU/L (0.5-5)

Which of the following is this patient's most likely diagnosis?

A. Clinically nonfunctioning pituitary adenoma
B. Histiocytosis
C. Metastasis
D. Nivolumab-induced hypophysitis
E. Prolactinoma

19.2. ANSWER: C) Metastasis

The key features in this vignette are the rapid growth of the mass and the presence of arginine vasopressin deficiency, which are most consistent with metastasis (Answer C). Arginine vasopressin deficiency occurs because the metastasis involves the posterior pituitary gland. Common cancers that metastasize to the sella include breast cancer, renal cell carcinoma, and lung cancer. This patient's history of renal cell carcinoma makes metastasis the most likely diagnosis.

Clinically nonfunctioning pituitary adenomas (Answer A) are usually slow growing and are rarely associated with arginine vasopressin deficiency

Histiocytosis (Answer B) is a sellar lesion that can cause arginine vasopressin deficiency, but histiocytosis is contrast-enhancing and is thus incorrect.

19.3. ANSWER: C) Metastasis

Nivolumab (Answer D) is an anti-PD-1 antibody that is used as immunotherapy, and it has been associated with hypophysitis. However, because this patient has a discrete mass and arginine vasopressin deficiency, and because hypophysitis is uncommon with PD-1 inhibitors (more common with CTLA-4 checkpoint inhibitors), nivolumab is an unlikely culprit. In addition, immunotherapy-induced hypophysitis is Usually associated with a hyperenhancing—not a hypoenhancing—mass on imaging, although this is a variable finding. Prolactinoma (Answer E) is unlikely given the modestly elevated serum prolactin concentration, rapid increase in tumor size, and presence of arginine vasopressin deficiency (rarely associated).

Educational Objective:

Differentiate metastasis from other pituitary mass lesions.

20.1. A 20-year-old ♂ has been diagnosed with a 2.5-inch clinically nonfunctioning pituitary macroadenoma that has caused chiasmal compression. Her preoperative evaluation reveals no evidence of acromegaly, Cushing's disease, or salt and water imbalance. She undergoes transsphenoidal surgery, which is uneventful. Twenty hours after surgery, she develops a marked increase in thirst and polyuria. Lab: Na: 152 mEq/L (136-142). Urine osmolality = 110 mOsm/kg (150-1150).

Which treatment options should be considered?

A. 1 L fluid restriction
B. DDAVP, 0.1 mg orally as needed for polyuria and hypernatremia
C. DDAVP, 10 mcg intranasally nightly
D. DDAVP, scheduled dosing, 0.2 mg orally twice daily
E. Tolvaptan, 15 mg orally once daily as needed

20.2. ANSWER: B) DDAVP, 0.1 mg orally as needed for polyuria and hypernatremia

This patient has an acute onset of arginine vasopressin deficiency. In this setting, the cause is central, due to vasopressin deficiency. The goal of therapy is to control the free water depletion from polyuria, as well as maintain comfort. DDAVP should be administered in a short-acting regimen, avoiding prescheduled dosing given the risk of hyponatremia from syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the following days as part of the triphasic response after surgery. Therefore, DDAVP should be administered as needed (0.1 mg orally, and higher doses of 0.2 to 0.3 mg may be necessary) (Answer B) or as subcutaneous aqueous DDAVP, 0.5 to 1.0 mcg (not offered as an option in this vignette).

20.3. ANSWER: B)

Scheduled dosing (Answer D) should be avoided. Administration of DDAVP immediately following endonasal surgery should be given through oral or parenteral routes. Intranasal administration (Answer C) would not be sufficiently absorbed given trauma to the mucosal membranes from surgery, but it may be considered in the future if arginine vasopressin deficiency persists and the mucosal membranes have healed.

Fluid restriction (Answer A) is contraindicated in these patients who are prone to dehydration and is used to treat hyponatremia.

Tolvaptan (Answer E) is an oral vasopressin receptor antagonist used for the treatment of severe hyponatremia, which is not present in this patient.

Educational Objective:

Manage arginine vasopressin deficiency following pituitary surgery.

21.1. A 72-year-old ♂ reports fatigue, weight gain, decreased libido, and some difficulty maintaining an erection. He has been well all his life until these symptoms began. He attributes his symptoms to aging, but his wife has urged him to be evaluated. Although he recently retired, he has not changed his lifelong pattern of little exercise.

Exam: no abnormalities. BMI: 28. Thyroid: not enlarged, no Cushingoid features. The patient is well virilized. BP: 140/92. Pulse: 60.

Lab: CBC: normal. Chemistry: normal. TSH: 0.5 mIU/L (0.5-5). FT4: 0.5 ng/dL (0.8-1.8). Cortisol (8 AM): 10 µg/dL (5-25). Total testosterone (8 AM): 221 ng/dL (300-900). LH: 2.1 mIU/mL (1-9). FSH 1.7 mIU/mL (1-13). Which tests is the most important next step?

A. α-Subunit measurement
B. Ferritin measurement
C. Pituitary-directed MRI
D. Serum free testosterone measurement
E. Urinary free cortisol measurement

21.2. ANSWER: C) Pituitary-directed MRI

This older man with fatigue, weight gain, decreased libido, and erectile function has a normal TSH level. A normal TSH level does not by itself rule out hypothyroidism because the hypothyroidism may be secondary. In fact, his free TSH level is low. His testosterone, LH, and FSH levels are slightly low but consistent with aging. However, the combination of central hypothyroidism and hypogonadism makes it It is important to rule out a mass in the pituitary/hypothalamic area with MRI (Answer C). Urinary free cortisol measurement (Answer E) can be helpful when evaluating high cortisol states, but it is not helpful in the opposite circumstance.

In this context, measuring free testosterone (Answer D) would not add much to the evaluation. Although an evaluation for hemochromatosis (Answer B) is reasonable, hypopituitarism resulting from hemochromatosis usually occurs at a much younger age. Elevated a-subunit (Answer A) would only point more strongly to the need for MRI, and if the a-subunit level is normal, it does not provide evidence for one to argue against performing imaging. Treatment with testosterone and levothyroxine, and possibly hydrocortisone, may be indicated once the diagnosis is confirmed.

Educational Objective: Evaluate hypopituitarism in older men

22.1. A 19-year-old ♂ is referred for gigantism. Height 208 cm. Weight: 124 kg, both of which are greater than the 97th percentile. His hands and feet are enlarged, and he has prognathism. A maternal uncle was thought to have had a pituitary adenoma of uncertain type. There is no known family history of calcium disorders or kidney stones. A GH 90 ng/mL does not suppress adequately during oral glucose tolerance testing.

Lab: IGF: 11233 ng/mL (147-527). Prolactin 26 ng/mL (4-23). Thyroid and adrenal axes, normal. Serum calcium, normal. He has a bitemporal visual field defect. MRI of the brain shows a 4.3 x 3.2 x 2.8-cm pituitary adenoma with suprasellar extension. Which germline pathogenic variant of the following genes is most likely responsible for the findings in this patient?

A. AIP (aryl hydrocarbon receptor interacting protein)
B. GNAS (GNAS complex locus)
C. PROPI (PROP paired-like homeobox 1)
D. PTTGI (pituitary tumor-transforming gene)
E. TEX19 (T-box 19) (previously TPIT)

21.2. ANSWER: A) AIP (aryl hydrocarbon receptor interacting protein)

A small number of germline pathogenic variants are implicated in somatotroph tumorigenesis. These include pathogenic variants in AIP (associated with isolated familial pituitary adenomas), MENI (associated with multiple endocrine neoplasia type 1), and PRKARIA (associated with the Carney complex). Germline inactivating pathogenic variants in AIP predispose individuals to pituitary tumors, especially somatotropinomas. Overall, approximately one-third of families with familial acromegaly harbor a germline AIP variant Furthermore, as many as 20% of individuals younger than 18 years who have apparently sporadic pituitary macroadenomas have a pathogenic germline AIP variant. Tumors associated with AIP pathogenic variants are large and are often diagnosed in childhood or early adulthood, hence the typical presentation with gigantism.

21.3. ANSWER: A) AIP (aryl hydrocarbon receptor interacting protein)

Importantly, these variants exhibit low penetrance, so the disorder may appear to skip generations or be noted in distant relatives. The patient described in this vignette fits the profile, and of the choices listed, a germline pathogenic variant in AIP (Answer A) would be the most likely culprit. PTTGI (pituitary tumor-transforming gene) (Answer D) is frequently overexpressed in many pituitary adenomas, particularly in aggressive tumors, due to its role in cell cycle regulation, tumor growth, and angiogenesis. However, PTTGI is not typically associated with familial pituitary adenoma syndromes, as it functions primarily as an oncogene involved in tumor progression and invasiveness. Even if this patient's tumor was aggressive, the absence of a known familial syndrome linked to PTTG1 variants makes this diagnosis unlikely. Thus, a PTTGI variant is unlikely.

21.4. ANSWER: A) AIP (aryl hydrocarbon receptor interacting protein)

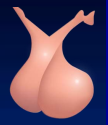
Postzygotic activating variants in the GNAS gene (Answer B) are responsible for McCune-Albright syndrome, which is characterized by polyostotic fibrous dysplasia, cutaneous pigmentation ("coast of Maine"), precocious puberty, hyperthyroidism, Cushing syndrome, and/or acromegaly due to somatotroph hyperplasia. Somatic activating point variants in GNAS represent one of the most common molecular alterations identified in sporadic somatotroph adenomas and are present in about 30% of sporadic GH-secreting tumors.

The protein encoded by PROPI (Answer C) is a transcription factor important in the differentiation of the GH and prolactin cell line.

Germline pathogenic variants in the TBX19 gene (Answer E), which encodes a transcription factor important for terminal differentiation of pituitary pro-opiomelanocortin-expressing cells, do not cause pituitary adenomas but instead cause a neonatal-onset form of congenital isolated ACTH deficiency.

Educational Objective:

Identify the genes associated with familial pituitary adenoma syndromes



The End

مراجعات البورد في الغدد

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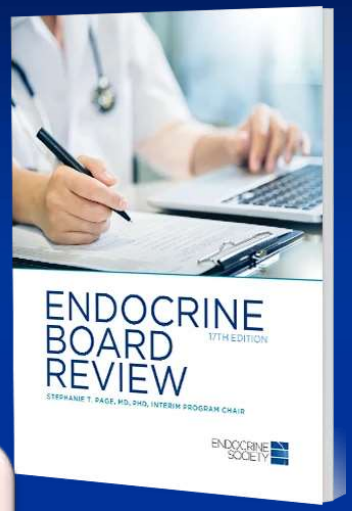
Thyroid: 1



Thyroid

الدكتور محمد الشعباني

1.1. A 23-year-old ♀ opera singer presents with a visible and palpable 2-cm thyroid nodule. US: solid, hypoechoic, 1.8-cm, right-sided thyroid nodule. TSH 1.75 mIU/L. FNA: benign thyroid nodule. She is instructed to monitor the nodule and return in 1 year. At her 1-year follow-up appointment, she reports that the nodule has grown, and she is concerned about its cosmetic appearance. She describes feeling like food sometimes gets "stuck" when she swallows. On US: the nodule has grown to 2.9 cm, but its appearance has not changed. The nodule is more prominent on physical exam than it was a year ago. FNA: benign. She would like to have the nodule removed but is concerned about the possibility of scarring and voice issues with surgery. Given the patient's concerns, which is the best next step in the management of this thyroid nodule?

A. Continued observation, as the nodule is <4 cm
B. Ethanol ablation
C. Radiofrequency ablation
D. Thyroid lobectomy in conjunction with a plastic surgeon
E. Thyroid lobectomy with a transoral approach

1.2. ANSWER: C) Radiofrequency ablation: Continued observation (Answer A) is not recommended because the patient is concerned about the nodule's more prominent appearance given her career as an entertainer. Additionally, she seems to be experiencing symptoms related to its increasing size. The best recommendation for this patient is radiofrequency ablation (Answer C) to shrink the nodule. This technique would avoid scar formation and, compared with surgery, is associated with a lower rate of complications, such as voice hoarseness. Ethanol ablation (Answer B) is more effective for cystic nodules than for solid nodules, and this patient has a solid nodule. Scheduling joint surgery with a plastic surgeon (Answer D) would be challenging and would not necessarily prevent a scar. Transoral lobectomy (Answer E) is an option to remove the nodule and prevent a scar; however, this technique has associated risks of vocal cord damage, hypothyroidism, bleeding, infection, and complications related to anesthesia

Educational Objective: We recommend radiofrequency ablation to shrink a growing solid thyroid nodule to avoid scarring and surgical complications, such as voice hoarseness, hypothyroidism, and hypocalcemia.

2.1. A 51-year-old ♂ is referred for follow-up of thyroid cancer. He initially presented to the emergency department with flu-like symptoms and was found to have a 1.9-cm nodule in the right lung base. Findings on lung biopsy were consistent with metastatic follicular thyroid cancer. Thyroid/US: showed a 1.5-cm right-sided nodule with abnormal lymph nodes. Final pathology after total thyroidectomy showed a 1.3-cm follicular thyroid cancer with 4-6 positive right-sided level III lymph nodes of 1.5 cm. Which is his AJCC (American Joint Committee on Cancer) staging and his ATA (American Thyroid Association) risk status?

A. Stage 2, intermediate risk
B. Stage 2, high risk
C. Stage 3, high risk
D. Stage 4, intermediate risk
E. Stage 4, high risk

2.2. ANSWER: B) Stage 2, 2, high-risk staging cancer

Care appropriately is important when counseling patients about their prognosis. Risk stratifying patients is a critical aspect of thyroid cancer management, as it determines further treatment with radioactive iodine and TSH goals. According to the AJCC (American Joint Committee on Cancer) eighth edition, thyroid cancer staging is based on age (table, following page). Age younger than 55 years is only stage 1 or stage 2 (thus, Answers C, D, and E are incorrect). Younger patients do relatively well in the setting of distant metastatic disease and have a higher 5-year survival, compared with the survival of older patients.

Stage 1 is disease in the neck (any T and any N). Stage 2 is diagnosed only if the thyroid cancer has spread with distant metastatic disease, M1. This patient was found to have an isolated lung metastasis. According to ATA (American Thyroid Association) thyroid cancer guidelines, patients are risk-stratified for cancer recurrence, and this is done independently of staging. A patient with distant metastatic disease is considered to have a high recurrence risk (thus, Answer B is correct and Answer A is incorrect). Stage 4 is always considered to be high risk

Educational Objective: Stage and risk stratify thyroid cancer at the time of diagnosis.

Differentiated thyroid cancer

When age at diagnosis is…	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
< 55 yrs	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥ 55 yrs	T1	N0/NX	M0	I
	T1	N1	M0	II
	T2	N0/NX	M0	I
	T2	N1	M0	II
	T3a/T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB

3.1. A 57-year-old ♂ has a history of tall cell variant of papillary thyroid cancer that was treated with total thyroidectomy and lymph node dissection and two doses of radioactive iodine (totaling 300 mCi). His thyroglobulin level has increased from 8-89 ng/mL (8-89 µg/L) with a suppressed TSH 0.03 mIU/L. He has normal findings on a ^{125}I whole-body scan, but a PET scan shows multiple bone lesions in the spine and the hip. He starts lenvatinib, 24 mg daily, and Ca 600 mg twice/day, which he takes with lunch and dinner. He reports that he took a biotin supplement for a week because he was worried about hair loss as an adverse effect, but he has not taken biotin for the past month. A TSH measurement two months later is 2.1 mIU/L He has been taking Levothyroxine 175 mcg/day, for the past two years. He takes it early in the morning and has never missed a dose. He has lost 3 kg since starting lenvatinib. Which of the following is the most likely cause of his increased TSH level?

A. Adverse effect of the tyrosine kinase inhibitor
B. Biotin interference
C. Levothyroxine absorption issues since starting calcium supplements
D. Poor adherence to levothyroxine treatment
E. Progression of metastatic bone disease

3.2. ANSWER: A) Adverse effect of the tyrosine kinase inhibitor

The most likely cause of the patient's increased TSH concentration is lenvatinib, a tyrosine kinase inhibitor (Answer A) that is known to accelerate thyroid hormone metabolism, leading to higher TSH levels over time. His TSH increased from 0.03 to 2.1 mIU/L, which is a mild but expected rise in patients on lenvatinib, indicating a gradual increase in thyroid hormone requirements. His levothyroxine dosage requires adjustment.

While the elevated TSH could be caused by poor adherence (Answer D), the patient reports taking levothyroxine regularly, and his TSH was previously suppressed. Absorption issues (Answer C) are unlikely, as he takes levothyroxine correctly in the morning, separate from calcium supplements. Also, impaired absorption would generally lead to a higher TSH concentration than that observed in this vignette. Biotin exposure over a month ago would not affect his current thyroid function tests (Answer B). Progression of metastatic bone disease (Answer E) is not associated with increased TSH levels.

Educational Objective:

Describe how tyrosine kinase inhibitors used to treat advanced thyroid cancer affect TSH and levothyroxine dosage requirements.

4.1. A 37-year-old ♀ presents for evaluation of a right-sided neck mass. Exam: 2-3-cm palpable mass is detected. Thyroid/US: 2.9-cm hypoechoic nodule with regular borders and no calcifications. FNA: Bethesda category V, suspicious for papillary thyroid cancer. She underwent lobectomy, and the final pathology is consistent with noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Her TSH concentration was 1.8 mIU/L before surgery, and it is 2.3 mIU/L one month after surgery. Which is best categorizes this patient's recurrence risk and recommended management?

Answer	Recurrence risk	Management recommendation
A	Intermediate	Completion thyroidectomy
B	High	Completion thyroidectomy followed by radioactive iodine treatment
C	Intermediate	Levothyroxine therapy, with gool THS of 0.5-2 mIU/L
D	Low	Nech US in 6-12 months
E	Low	Serial thyroglobulin measurement every 6 months

4.2. ANSWER: D) Low recurrence risk; neck 4 ultrasonography in 6 to 12 months

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a low-risk thyroid tumor with an excellent prognosis after surgical removal. It is no longer classified as thyroid cancer, and aggressive treatments, such as completion thyroidectomy or radioactive iodine therapy (Answers A and B), are not necessary. Follow-up ultrasonography in 6 to 12 months (Answer D) would be appropriate at this time.

Although postlobectomy TSH monitoring is appropriate, suppressive therapy (Answer C) is not indicated because NIFTP is nonmalignant. Additionally, the patient's TSH concentration may continue to decrease over the next couple of months. Thyroglobulin monitoring every 6 months (Answer E) would not be recommended, as this patient has had a lobectomy, and this strategy is no longer recommended.

Educational Objective:

Risk stratify noninvasive follicular thyroid neoplasm with papillarylike nuclear features (NIFTP) and recommend surveillance

5.1. A 47-year-old ♂ was diagnosed with medullary thyroid cancer at the age of 19 years, at the same time that other family members were also diagnosed. Genetic testing confirmed a RET pathogenic variant consistent with multiple endocrine neoplasia type 2A. Over the years, his medullary thyroid cancer progressively worsened, He currently has three bone metastases. Findings on follow-up PET indicate that the disease continues to progress. Which is the best medication to prescribe now to treat this patient's thyroid cancer?

A. Cabozantinib
B. Lenvatinib
C. Selpercatinib
D. Sorafenib
E. Vandetanib

5.2. ANSWER: C) Selpercatinib

The preferred first-line treatment for advanced, progressive medullary thyroid cancer (MTC) associated with RET pathogenic variants is Selpercatinib (Answer C), a highly selective RET kinase inhibitor that has demonstrated superior efficacy and tolerability compared with older multikinase inhibitors. RET pathogenic variants are common in multiple endocrine neoplasia type 2A-associated MTC, and since this patient has had progressively worsening disease over decades, a targeted RET inhibitor would be the most effective option. Clinical trials have shown that Selpercatinib significantly improves progression-free survival and overall response rates in patients with MTC associated with RET pathogenic variants.

Older multikinase inhibitors, such as Vandetanib (Answer E) and Cabozantinib (Answer A), while previously used and approved for MTC, They have more off-target effects and lower efficacy than selective RET inhibitors.

Other tyrosine kinase inhibitors, such as lenvatinib (Answer B) and sorafenib (Answer D), are approved for differentiated thyroid cancers, but they lack efficacy in MTC and are not FDA-approved for this indication.

Educational Objective:

Recommended treatment for advanced medullary thyroid cancer in patients with RET pathogenic variants.

6.1. A 27-year-old ♀ involved in a motor vehicle crash undergoes neck CT, which identifies a right-sided thyroid nodule. Thyroid/US: 1.35 x 1.03 x 1.6-cm, solid, hypoechoic nodule with regular borders and no microcalcifications. Which is the best classification and management of this nodule?

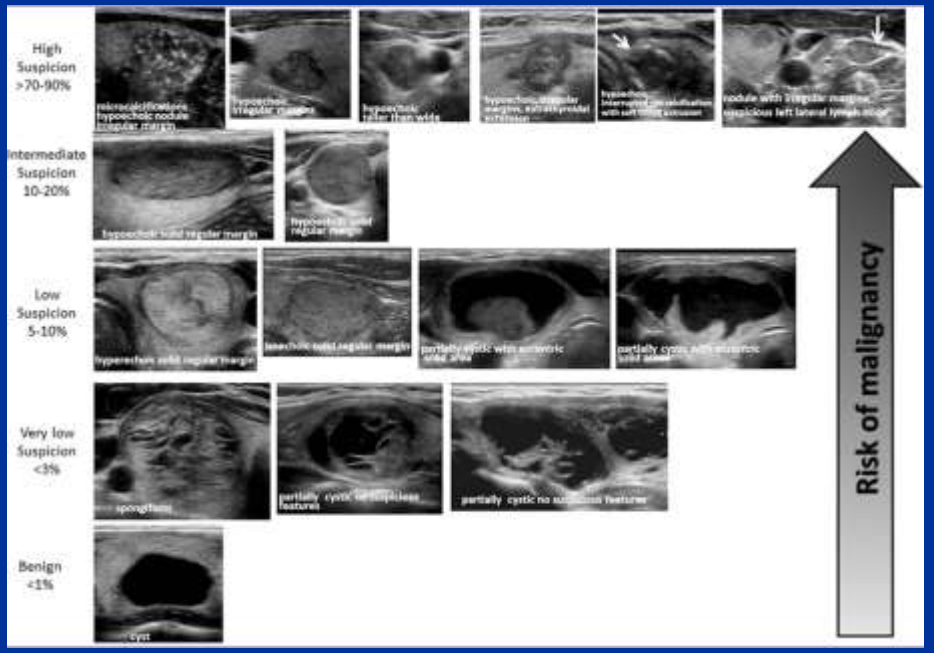
Answer	Suspicion for malignancy	Next step in management
A	High	FNA biopsy
B	Intermediate	FNA biopsy
C	Intermediate	Repeat US in 6-12 months
D	Low	FNA biopsy
E	Low	Repeat US in 6-12 months

6.2. ANSWER: B) Intermediate suspicion, recommend FNA biopsy

The key ultrasonography findings of this thyroid nodule are hypoechogenicity, regular borders, no microcalcifications, and solid composition. Hypoechogenicity increases suspicion for malignancy, while the absence of microcalcifications and the presence of regular margins are reassuring features. According to the American Thyroid Association (ATA) guidelines, this nodule falls into the intermediate-suspicion category (thus, Answers A, D, and E are incorrect). For intermediate-risk nodules, FNA biopsy is recommended for nodules 1.0 cm or larger (Answer B), rather than simply monitoring with repeat thyroid ultrasonography in 6 to 12 months (Answer C). Since this nodule measures 1.6 cm, it meets the criteria for biopsy to further assess malignancy risk.

TI-RADS criteria (Thyroid Imaging, Reporting, and Data System) are also used to classify thyroid nodules based on the general categories of composition, shape, margins, echogenic foci, and echogenicity (see figure, following page). This nodule would be a TI-RADS 4 nodule (4 points: hypoechoic and (solid). Based on the TI-RADS criteria, FNA biopsy is recommended for nodules larger than 1.5 cm.

Educational Objective: Risk stratify a thyroid nodule and determine whether FNA biopsy is required.



7.1. A 53-year-old ♀ is diagnosed with right-sided intraductal breast cancer. As part of her workup, she undergoes a PET scan, which reveals a PET-positive thyroid nodule on the right side. Subsequent thyroid/US identifies a right-sided, 1.2-cm, solid, hypoechoic nodule with regular borders. No abnormal lymphadenopathy is noted
Which is the best risk stratification and next step in management?

Answer	Risk of cancer base on PET	Next step in management
A	Increased	FNA biopsy
B	Decreased	FNA biopsy
C	No effect	Repeat US/6-12 months
D	Increased	Repeat US/6-12 months
E	Decreased	Repeat US/6-12 months

7.2. ANSWER: A) Increased risk, recommend FNA biopsy

PET-positive thyroid nodules are associated with a higher risk of malignancy (30%-50%) than incidental thyroid nodules found on ultrasound alone (thus, Answers B, C, and E are incorrect). FNA biopsy is recommended for thyroid nodules larger than 1 cm, and this patient's nodule is 1.2 cm. The best next step in her management is FNA biopsy (thus, Answer A is correct and Answer D is incorrect). Additionally, based on American Thyroid Association criteria, this patient has an intermediate-risk thyroid nodule that is solid and hypoechoic with no other features associated with malignancy.

Educational Objective:

Assess the risk of malignancy for PET-positive thyroid nodules and recommend the best follow-up

8.1. A 65-year-old ♀ presents for follow-up. She underwent total thyroidectomy 5 years ago for papillary thyroid cancer. Pathology showed a 4.3-cm, left-sided tumor (tall cell variant) without extrathyroidal extension or vascular invasion. Six of 11 unilateral lymph nodes were involved. Her tumor was classified as stage II (T3N1bM0). She was subsequently treated with radioactive iodine, with a posttreatment scan showing uptake in the thyroid bed and in a left-sided cervical node. A follow-up whole-body scan 1 year after the ablation was negative. She currently feels well. Lab: TSH 0.01 mIU/L. FT4: 2.1 ng/dL (0.8-1.8). Thyroglobulin <0.1 ng/mL. Thyroglobulin antibodies: negative. Recent neck/US shows two left-sided level IV lymph nodes and no thyroid remnant tissue. Both lymph nodes are oblong with visible helix, regular margins, and no microcalcifications, measuring 0.5 cm and 0.4 cm. Which is the most appropriate next step?

A. Continue current levothyroxine, order PET
B. Continue current levothyroxine, perform FNA biopsy of the largest lymph node
C. Decrease levothyroxine dosage, schedule radioactive iodine whole-body scan
D. Decrease levothyroxine dosage, schedule repeated TSH 6-8 weeks
E. Increase levothyroxine dosage, schedule US in 6 months

8.2. ANSWER: D) Decrease levothyroxine dosage, schedule repeated TSH measurement in 6-8 weeks: Following surgery and radioactive iodine ablation, this patient's tumor would initially have been staged as intermediate risk In addition, the tall cell variant of papillary thyroid cancer is known to be aggressive. However, she has had an excellent response to therapy, with no current evidence of disease based on undetectable unstimulated thyroglobulin and ultrasonography showing only benign-appearing lymph nodes. Current American Thyroid Association guidelines recommend continual modification of risk status based on new information obtained during follow-up. An excellent response to therapy, defined as negative imaging and a suppressed serum thyroglobulin < 0.2 ng/mL (<0.2 µg/L) or stimulated thyroglobulin < 1 ng/mL (<1 µg/L) in the absence of thyroglobulin antibodies, should lead to both a decrease in the level of TSH suppression and a lessening of the intensity and frequency of follow-up.

8.3. ANSWER: D) A TSH target in the low-normal range would be reasonable for this patient. Thus, maintaining or increasing the TSH-suppressive levothyroxine dosage (Answers A, B, and E) is incorrect. There is no role for another radioactive iodine whole-body scan (Answer C), given evidence of her excellent response to therapy and the previously negative whole-body scan. There is no indication for FNA biopsy of the lymph nodes, which are normal appearing. American Thyroid Association guidelines recommend FNA biopsy of abnormal-appearing lymph nodes that measure at least 0.8 cm in smallest dimension. The best course of action is to decrease her levothyroxine dosage with a TSH goal of 0.5 to 2.0 mIU/L and to measure TSH in 6 to 8 weeks (Answer D).

Educational Objective: Explain restaging in the setting of thyroid cancer and guide appropriate surveillance and treatment in a patient with an excellent response to thyroid cancer therapy.

9.1. A 27-year-old man with no relevant medical history is noted to have a goiter and is referred for further evaluation.

Exam: Pulse: 90. He has a diffuse goiter, twice normal size, without nodules or bruit. Deep tendon reflexes are normal, and he has no tremor.

Lab: FT4: 2.7 ng/dL (0.8-1.8). TT4: 14.1 µg/dL (5.5-12.5). TT3: 300 ng/dL (70-200). TSH 3.8 mIU/L (0.5-5). α-subunit: 0.3 ng/mL (<1.2). There is a linear pattern of TSH values with serial dilution.

Which is the most likely explanation for this patient's lab results and clinical presentation?

A. Heterophilic antibody interference with the TSH assay
B. Surreptitious use of thyroid hormone
C. T4, antibody interference with the FT4, assay
D. Thyroid hormone resistance
E. TSH-producing pituitary adenoma

9.2. ANSWER: D) Thyroid hormone resistance

This patient has discordant TSH and free TSH values, suggesting inappropriate TSH release. The a-subunit-to-TSH molar ratio less than 1.0 favors thyroid hormone resistance (Answer D) rather than a TSH-producing pituitary tumor (Answer E). The prevalence of thyroid hormone resistance is about 1 in 40,000 live births

Another possible cause is heterophilic antibodies (Answer A), but serial dilutions would not be expected to yield linear results if these were present T antibodies (Answer C) tend to increase the measured value of free T, but do not affect total T and TSH.

Surreptitious use of thyroid hormone (Answer B) might cause thyrotoxicosis, but this would not produce this pattern of thyroid function test results or the diffuse goiter.

Educational Objective:

Identify clinical features of thyroid hormone resistance.

10.1. A 32-year-old ♀ with obesity was found to have a slightly elevated TSH during her evaluation before bariatric surgery. BMI 44. She has made longstanding efforts to reduce her weight, including dietary restriction, exercise, and medical therapy that she could not tolerate. At the weight-loss center she attends, health professionals have deemed her a good candidate for bariatric surgery. A review of her medical records shows that she also had a slightly elevated TSH value documented 2 years ago but had a normal TSH value 10 years ago. She has no personal history of thyroid disease, has never taken thyroid hormone therapy, and has no family history of obesity or thyroid disease. Findings on thyroid examination are unremarkable. The patient is ready to proceed with surgery, but she has been referred because of her elevated serum TSH value.

Lab: TSH 6.1 mIU/L (0.5-5) (prior TSH values: 5.7 mIU/L [2 years ago] and 3.4 mIU/L [10 years ago]). FT4: 1.1 ng/dL (0.8-1.8). TT3: 137 ng/dL (70-200).

TPO antibodies: negative. Which is the best advice for this patient?

A. Hold surgery and begin levothyroxine therapy
B. Hold surgery and measure serum leptin
C. Hold surgery pending repeat TSH in 2 to 3 months
D. Proceed with surgery
E. Recommend sleeve gastrectomy instead of Roux-en-Y gastric bypass

10.2. ANSWER: D) Proceed with surgery

There are cross-sectional studies demonstrating that TSH values are positively associated with obesity and BMI values, such that in one study an increase in TSH values was observed for every quartile increase in BMI. In another study, approximately 10% of patients with elevated BMIs also had TSH values above the upper limit of the reference range, compared with 5.8% of those with a normal weight. BMI-specific TSH reference ranges have been proposed

It has also been shown that bariatric surgery, with associated weight loss, normalizes TSH values. Free TSH values, however, do not appear to be associated with BMI and are not affected by weight loss following bariatric surgery. Total TSH levels may decrease after bariatric surgery. Decreased leptin stimulation of the thyroid axis with a decrease in serum TSH has been proposed to occur after weight loss.

10.3. ANSWER: D) Proceed with surgery

This patient's mildly elevated TSH is most likely a consequence of obesity, especially because TPO antibodies are not elevated. There is no rationale for delaying bariatric surgery based on her thyroid function tests, and her surgery can proceed as planned (Answer D). Significant weight loss is not associated with treatment of mild hypothyroidism. Therefore, levothyroxine (Answer A) would not reduce this patient's degree of obesity Further laboratory evaluation with measurement of leptin (Answer B) is not actionable. Leptin levels may decrease after bariatric surgery, but assessment of these levels before bariatric surgery does not provide additional useful information. Repeating TSH measurement (Answer C) would most likely show continued elevation, as she had a previously elevated TSH value 2 years ago. Her TSH concentration is not useful for determining the most appropriate bariatric surgery to choose (Answer E).

Educational Objective: Explain how obesity can alter TSH and that this is likely to be a consequence rather than a cause of obesity.

11.1. A 64-year-old ♂ is found to have T3 11 Nib papillary thyroid cancer following thyroidectomy and lateral and central compartment lymph node dissection. Radioactive iodine remnant ablation is planned. One day after starting his low-iodine diet, he develops severe shortness of breath and goes to the emergency department where a chest CT with intravenous contrast shows no pulmonary embolism. He calls the endocrine clinic the next day with this update. Which is the best next step in this patient's management?

A. Continue the low-iodine diet for an extra week (3 weeks total) and then proceed with radioactive iodine ablation
B. Defer radioactive iodine for 1-3 months after contrast exposure
C. Maintain current instructions and proceed with radioactive iodine ablation as planned
D. Measure urinary iodine after completing the diuretic and treat with radioactive iodine if urine iodine is low.
E. Recommend increased fluid intake, initiate daily furosemide, and proceed with radioactive iodine ablation as planned.

11.2. ANSWER: B) Defer radioactive 11-iodine for 1 to 3 months after contrast exposure: The cornerstones of preparation for radioactive iodine ablation are generally considered to include serum TSH elevation using recombinant human TSH and iodine depletion by adhering to a low-iodine diet. If a spot urine iodine test is checked to verify that iodine levels have been sufficiently lowered, urinary iodine excretion < 50 µg/g creat is considered evidence of success. The problem that may be encountered in this patient is that the iodine load he was exposed to as a result of the iodinated contrast media could contain 1.5-37 g of iodine. Some studies suggest that urinary iodine may return to baseline 4-6 weeks after iodinated contrast exposure. The time 4 weeks in athyrotic individuals and 6 weeks or even longer in those with intact thyroid glands in whom the thyroid concentrates iodine and thus allows whole-body iodine retention In those with kidney insufficiency, iodine clearance may be slower.

11.3. ANSWER: B)

Moreover, there are also data suggesting that despite the return to "baseline" urinary iodine concentration, a delay after contrast exposure for at least 3 to 4 months (Answer B) may be associated with better response rates to radioactive iodine in patients with intermediate-risk thyroid cancer. Animal models suggest that iodinated contrast media can reduce iodine uptake in the thyroid even after iodine has cleared, perhaps by decreasing sodium-iodide symporter expression. If the goal is to achieve a low urinary iodine concentration, rather than simply a normal one, maintaining the same instructions and schedule for the patient (Answer C) may be inadvisable. Hydration and diuretic regimens (Answer E) have been used to potentially prevent radiocontrast-induced nephropathy and have also been used to clear iodine that is present because of a contrast load.

11.4. ANSWER: B)

However, this has not been evaluated as a strategy and theoretically could increase the risk of hyponatremia during the low-iodine diet. Given the high urine load, it is unlikely that two weeks of the low-iodine diet would significantly lower his iodine level, and therefore it is not recommended to continue the diet for two weeks and check iodine levels (Answer D).

It is possible that a longer duration of a low-iodine diet for three weeks (Answer A) may help lower the iodine load caused by the iodinated contrast media. However, the success of this approach has not been documented.

Educational Objective:

Explain how exposure to iodinated contrast media provides a significant iodine load and may necessitate a delay in radioactive indine administration

11.3. ANSWER: B) Moreover, there are also data suggesting that despite the return to "baseline" urinary iodine concentration, a delay after contrast exposure for at least 3 to 4 months (Answer B) may be associated with better response rates to radioactive iodine in patients with intermediate-risk thyroid cancer. Animal models suggest that iodinated contrast media can reduce iodine uptake in the thyroid even after iodine has cleared, perhaps by decreasing sodium-iodide symporter expression.

If the goal is to achieve a low urinary iodine concentration, rather than simply a normal one,

maintaining the same instructions and schedule for the patient (Answer C) may be inadvisable

Hydration and diuretic regimens (Answer E) have been used to potentially prevent radiocontrast-induced nephropathy and have also been used to clear iodine that is present because of a contrast load. However, this has not been evaluated as a strategy and theoretically could increase the risk of hyponatremia during the low-iodine diet.

12.1. A 36-year-old ♀ presents for ongoing management of thyroid disease Cancer. She underwent total thyroidectomy to treat papillary thyroid cancer 2 months ago. The pathology report described a 2.4-cm focus of classic papillary thyroid cancer with 2 additional foci of 1.5 and 0.7 cm, extension of the tumor into perithyroidal soft tissue, and close proximity of the tumor to the resection margin (0.1 cm). 21 of 24 central compartment lymph nodes contained thyroid cancer. The patient regularly takes levothyroxine. Her medical history includes end-stage kidney disease due to glomerulonephritis for which she undergoes hemodialysis. Exam: and postoperative US do not detect any abnormal lateral cervical nodes.

Based on her pathology findings, ablation with radioactive iodine is recommended to decrease her risk of thyroid cancer recurrence. A diagnostic scan Followed by selection of appropriate 131I activity is suggested.

Which of the following is the best approach for this patient?

A. Administer I activity that is 50% of standard activity
B. Administer I activity that is 10% of standard activity
C. Administer ^{123}I
D. Administer standard I activity after 4 weeks of a low-iodine diet
E. Monitor with serial ultrasonography

12.2. ANSWER: A) Administer 1 activity that is 50% of standard activity

Following radioactive iodine administration, iodine that is not taken up into the thyroid remnant or thyroid cancer tissue is cleared from the body primarily via the kidneys and excreted in the urine. This can be illustrated during posttherapy scanning when iodine accumulation in the bladder can be visualized. In a biokinetic model developed using in vivo gamma camera scanning, the metabolism and clearance of iodine were demonstrated in 6 patients with thyroid cancer and normal kidney function, as activity was demonstrated successively in the stomach, body fluid, whole body, bladder, and thyroid remnant. In an anuric patient with end-stage kidney disease, iodine cannot be cleared by the usual routes, and there is potential for excessive exposure of the whole body and bone marrow. In this particular patient, administration of radioactive iodine is indicated because of her multifocal tumor with extrathyroidal extension and significant lymph node involvement.

12.3. ANSWER: A) Administer 1 activity that is 50% of standard activity

Therefore, monitoring with serial ultrasonography is not a recommended standard of care (Answer E). End-stage kidney disease is not a contraindication to treatment with radioactive iodine. If radioactive iodine ablation is intended, administering radioactive iodine as the ^{123}I isotope (Answer C) would not suffice because this isotope can only be used for imaging and not for ablation, as it emits only gamma particles that can be imaged with a gamma camera (not destructive beta particles). The 131 isotope, however, emits both gamma and beta particles. Regarding the need for an extended Duration of a low-iodine diet (Answer D): This has not been well studied, but the use of an empiric activity of radioactive iodine would most likely lead to excessive bone marrow exposure.

12.4. ANSWER: A) Administer 1 activity that is 50% of standard activity

Case examples of patients with end-stage kidney disease who were treated with radioactive iodine for thyroid cancer are shown (see table). Although approaches varied in these case reports, in general, patients were treated with reduced activities, compared with the anticipated empiric activity. However, there are other case reports in which patients were treated with higher than standard activities. The activity chosen depends strongly on the dialysis schedule, generally with hemodialysis being pursued 24 to 48 hours after radioisotope administration to reduce whole-body and bone marrow exposure. The administration of radioactive iodine to a patient receiving dialysis requires careful planning and precautions to avoid exposure of the caring staff For the patient and while performing dialysis, appropriate measures should be taken to avoid contamination of dialysis equipment.

12.5. ANSWER: A) Administer 1 activity that is 50% of standard activity

Based on the reported mathematical modeling and dosimetric calculations, a reasonable approach is to administer 50% of standard activity (Answer A), or, if available, to determine the activity based on dosimetric calculations. Giving 10% of standard activity (Answer B) would most likely not be sufficient to provide effective ablation.

Educational Objective:

Explain that radioactive iodine is excreted via the kidneys and that a reduction of radioactive iodine activity is required for a patient with thyroid cancer and end-stage kidney disease.

12.6. ANSWER: A) Administer 1 activity that is 50% of standard activity

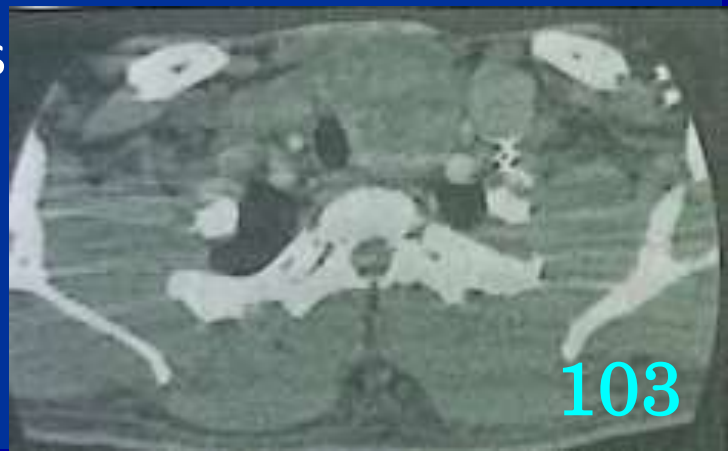
Table. Examples of Radioactive Iodine Administered for Ablation Under Hypothyroid Conditions in Patients With End-Stage Kidney Disease

Author, year (number of cases)	Hemodialysis or peritoneal dialysis	Activity selected (mCi)	How determined
Willegaignon 2010: 1 case.	Peritoneal	100	Dosimetry
Holst 2005: 1 case	Hemodialysis	98	60% reduction
Bhot 2017: 1 case	Hemodialysis	50	Based on AUC for ^{131}I
Jiminez 2001: 3 cases	Hemodialysis	75 87 120	dosimetry
Yeyin 2015: 3 cases	Hemodialysis	50 50 75	50% reduction
Alevizoki 2006: 5 cases	Hemodialysis	30 35 35 40 70	40-50%
Murcutt 2008: 1 case	Hemodialysis	81	No reduction

13.1. A 52-year-old ♀ is referred for Ra evaluation of a neck mass. The patient notes dysphagia with solid foods and positional dyspnea when lying on her right side. Her medical history is noncontributory. Exam: she has a large goiter extending below the clavicle on the left side. TSH: 0.5 mIU/L, and radioiodine uptake is 13% at 24 hours. US: multinodular goiter with confluent isoechoic nodules throughout. Results from FNA biopsy of the largest nodule are benign. Noncontrast CT of the neck is shown (see image).

Which of the following is the best next step in this patient's management?

A. Levothyroxine suppressive therapy
B. No intervention until symptoms progress
C. Radioiodine therapy using rhTSH
D. Thermal ablation therapy
E. Thyroidectomy via collar incision



13.2. ANSWER: E) Thyroidectomy via collar incision

CT shows a substernal goiter with a mass effect on the trachea. The patient is symptomatic, with positional dyspnea, most likely due to tracheal compression by the asymmetrically enlarged thyroid when she lies on her side. She also has dysphagia suggesting the goiter is impinging her esophagus. More than 90% of substernal goiters can be delivered through a collar incision (Answer E). The remaining therapeutic options listed are less helpful. Specifically, this euthyroid patient's thyroid mass is unlikely to respond significantly to levothyroxine suppressive therapy (Answer A), and she would be at risk for iatrogenic hyperthyroidism. Radioactive iodine therapy with the assistance of recombinant human TSH (Answer C) in a patient with an intact thyroid should be carefully monitored and is potentially dangerous due to a release of thyroid hormone from the gland and temporary swelling of the thyroid gland under the influence of recombinant human TSH.

13.3. ANSWER: E) Thyroidectomy via collar incision

This might be considered a potential option in a patient who is not a surgical candidate. This patient is healthy and not in an older age group that would preclude definitive resection of her goiter. Thermal ablation (Answer D) would not reduce the size of this very large substernal goiter, which cannot be addressed by ultrasound-guided ablation techniques No intervention (Answer B) would be inappropriate given her symptomatic disease. An analysis of studies of goiter treatment either by surgical resection or with the use of radioactive iodine therapy shows that both approaches relieve pressure on surrounding structures and improve respiration and swallowing. In a healthy 52-year-old patient, surgery would certainly provide definitive therapy for her compressive symptoms.

Educational Objective:

Devise a treatment approach to a symptomatic substernal goiter.

14.1. A 27-year-old ♀ presents with a 2.0-cm nodule at the lower pole of the left thyroid lobe (image). FNA biopsy reveals watery, clear, colorless fluid. Which is the most likely diagnosis?

A. Aberrant salivary gland cyst
B. Branchial cleft cyst
C. Follicular thyroid cancer
D. Parathyroid cyst
E. Thyroglossal duct cyst

14.2. ANSWER: D) Parathyroid cyst

The classic description of parathyroid cyst fluid is clear, colorless liquid that contains extremely high PTH levels. When such fluid is obtained during biopsy of what appears to be a thyroid nodule, the fluid should be sent for PTH analysis. Parathyroid cysts (Answer D) can be functioning or nonfunctioning. Serum calcium and PTH levels may also be elevated if the patient has hyperparathyroidism due to a functioning parathyroid cyst. Surgery is generally recommended for functioning parathyroid cysts, whereas conservative therapy, aspiration, sclerotherapy, or surgery can be pursued for nonfunctioning cysts

Branchial cleft cysts (Answer B) are located laterally in the neck, and thyroglossal duct cysts (Answer E) are generally located at the midline adjacent to the hyoid bone.

Follicular thyroid cancer (Answer C) is not generally prone to cystic change, but conversely, this is a common finding in patients with papillary thyroid cancer.

Aberrant salivary gland tissue with cystic degeneration (Answer A) is a very rare disorder, and cases do not occur within or juxtaposed to the thyroid.

Educational Objective: Recognize the typical presentation of a parathyroid cyst.

15.1. A 48-year-old woman seeks evaluation after a 3.47 x 1.12 x 1.85-cm thyroid nodule was noted incidentally on CT. She is not aware of anterior neck changes. Her serum TSH concentration is 2.37 mIU/L. She has no history of head or neck radiation and no family history of thyroid cancer. Ultrasonography of the right thyroid lobe is shown (see image). Which best approximates her risk for malignancy?

A. < 1%
B. < 3%
C. 5-10%
D. 10-20%
E. 70-90%

15.2. ANSWER: B) <3% The image shows a spongiform nodule with clearly defined margins. A nodule's appearance is defined as spongiform when more than half of the nodule's volume is composed of microcystic spaces. This ultrasound pattern strongly suggests that the nodule is benign, with less than a 3% risk of malignancy (Answer B). Because of the low malignancy risk in these nodules, current American Thyroid Association guidelines recommend considering FNA biopsy for spongiform nodules 2 cm or larger, but note that these can also be followed up with observation without proceeding to FNA biopsy Intermediate-suspicion patterns are associated with a 10% to 20% risk of malignancy (Answer D) and include hypoechoic nodules with smooth margins but without microcalcifications, extrathyroidal extension, or a taller-than-wide shape.

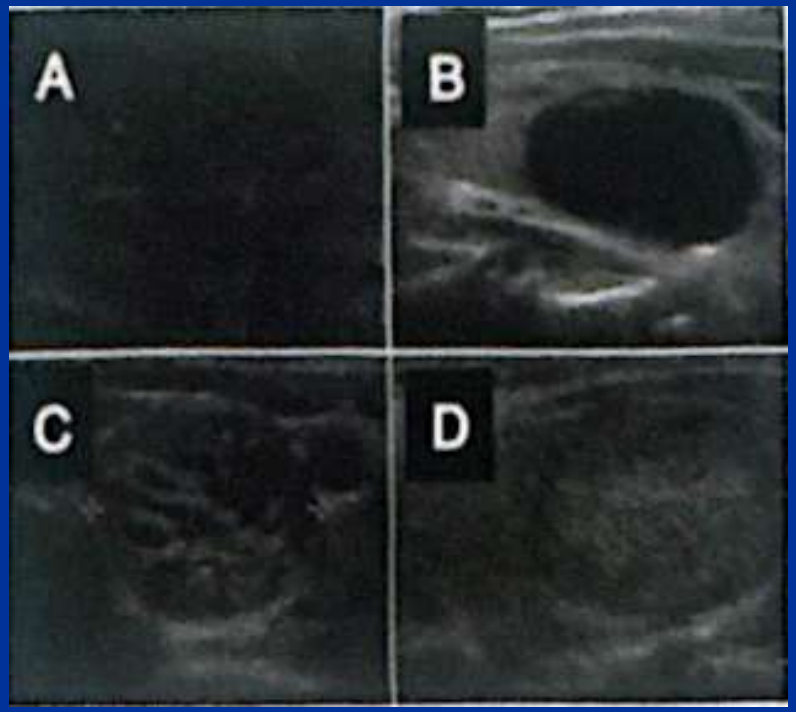
15.3. ANSWER: B) <3% The image shows a spongiform nodule

Low-suspicion nodules are those that are isoechoic or hyperechoic without microcalcifications, irregular margins, or a taller-than-wide shape. Low-suspicion nodules have a 5-10% risk of malignancy (Answer C). Nodules with a high risk of malignancy of 70% to 90% (Answer E) include those that are hypoechoic with irregular margins, microcalcifications, a taller-than-wide shape, or evidence of extrathyroidal extension. Purely cystic nodules with no solid component are considered benign with < 1% risk of malignancy (Answer A). The malignancy risk of these nodules overlaps with the estimate of < 3% described for spongiform nodules in the 2015 American Thyroid Association guideline for management of thyroid nodules and thyroid cancer. However, due to the negligible malignancy risk of < 1%, no biopsy is recommended unless needed to manage compression or cosmetic issues caused by the cystic nodule.

Educational Objective: Interpret the malignancy risk associated with different thyroid ultrasonographic patterns

16.1. What is the suspicion of malignancy among the figures below, with a risk of 5-10%?

A. Figure A
B. Figure B
C. Figure C
D. Figure D



16.2. ANSWER: D) Figure D 16 Thyroid nodules can be evaluated using ultrasonography to determine their risk of malignancy based on characteristics, such as echogenicity, border characteristics, presence of calcifications, and internal composition. An analysis of the different types of nodules depicted in Answers A, B, C, and D, along with their associated malignancy risks, is shown in the table.

Table. Summary of Malignancy Risk Based on Ultrasound Features

Figure	Nodule Type	Features	Malignancy rate
A	Hypoechoic with irregular borders and macrocalcifications	Highly suspicious	70-90%
B	Cystic (anechoic)	Benign	< 1%
C	Spongiform with irregular borders	Very low suspicion	< 3%
D	Hyperechoic with intact halo	Low suspicion	5-10%

Educational Objective:

Identify ultrasound patterns characteristic of benign and malignant nodules

17.1. A 33-year-old ♀ undergoes Thyroidectomy after thyroid cancer is diagnosed. Pathology shows multifocal intrathyroidal papillary thyroid cancer. Three foci are identified: a 0.9-cm focus in the right lobe and two foci of 3 mm and 7 mm in the left lobe. She is negative for BRAF V600E. No abnormal lymph nodes are identified at the time of surgery. The patient initiates thyroid hormone replacement and returns to discuss whether radioactive remnant ablation is indicated. Her postoperative thyroglobulin: 0.3 ng/mL while taking levothyroxine to achieve a TSH: 0.3 mU/L. A joint decision is made that, due to her low risk, remnant ablation with radioactive iodine is not indicated. Cervical US 1 year does not identify any abnormal lymph nodes, and thyroglobulin is undetectable. She is lost to follow-up for 3 years, at which time neck US: 1.5-cm left abnormal level VI lymph node with a thyroglobulin: 4 ng/mL (4 µg/L) and a TSH 0.65 mIU/L. Which best describes the recurrence rate in this patient at the time of initial diagnosis?

A. 1%
B. 5%
C. 10%
D. 30%
E. 50%

17.2. ANSWER: B) 5%: At initial presentation, the patient described in this vignette would have been classified as being at low risk according to the American Thyroid Association. Her largest tumor focus was 1.5 cm, and there was no documented extrathyroidal extension or cervical lymph node involvement. Given that she was at low risk, she was not treated with radioactive iodine. Recurrence risk categories are as follows: low risk, 1% to 5%; intermediate risk, 10% to 30%; and high risk, 30% to 55%. Unifocal papillary thyroid cancer has a recurrence risk of 1% (Answer A), but this patient has multifocal papillary thyroid cancer, which is associated with a slightly higher risk of 4% to 6% (Answer B). Intrathyroidal BRAF-positive papillary thyroid cancer smaller than 4 cm has a 10% risk (Answer C), but this patient is BRAF-negative. Large lymph nodes (>3 cm) are associated with a 30% recurrence risk (Answer D). This patient had no lymph nodes on exam and was not treated with radioactive iodine.

Follicular thyroid cancer with vascular invasion has a recurrence risk of 30% to 55% (Answer E), but this patient has papillary thyroid cancer, not follicular thyroid cancer.

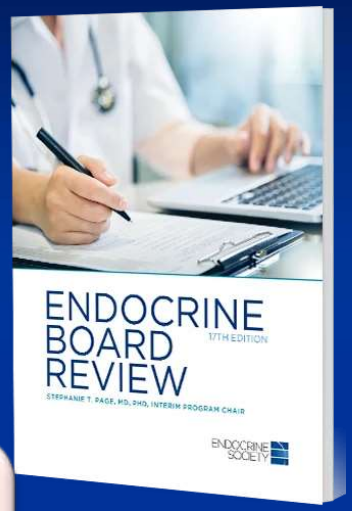
Educational Objective: Describe the recurrence risk at the time of diagnosis for low-risk multifocal papillary thyroid cancer

مراجعات البورد في الغدد

2

EBR.17

Thyroid: 2



Thyroid

الدكتور محمد الشعباني

1.1. A 75-year-old ♀ is evaluated in the emergency department for worsening altered mental status over the last 24 hours. She is accompanied by her son, who states that the patient has not received routine medical care for many years. She has no known relevant medical history and takes no medications. Her son reports that for the last several days, she has had a fever, a cough producing yellow sputum, and shortness of breath. When she started becoming more confused, he brought her to the emergency department for evaluation.

Exam: T°: 35.5°C. BP: 88/66. Pulse: 108. She has a slight goiter. Neurologic exam: she groans to the sternal rub. She has diminished breath sounds over the right lower lung lobe. There is periorbital edema.

Lab: TSH: 120 mIU/L (0.5-5). FT4: 0.3 ng/dL (0.8-1.8). Serum cortisol: 2.8 µg/dL (5-25).

Empiric antibiotics are started while awaiting blood culture results and chest imaging.

Which of the following is the best next step in this patient's management?

A. IV Levothyroxine and admission to the medical intensive care unit
B. Oral Levothyroxine and discharge home
C. Oral Liothyronine and admission to the general medical floor
D. Stress-dose IV hydrocortisone, IV Levothyroxine, and admission to general medical floor
E. Stress-dose IV hydrocortisone, IV Levothyroxine, and admission to intensive care unit

1.2. ANSWER: E) Stress-dose IV hydrocortisone, IV Levothyroxine therapy, and admission to the medical intensive care unit

This patient has developed decompensated severe hypothyroidism, also called myxedema coma, in the context of likely pre-existing, untreated hypothyroidism and acute pneumonia. Myxedema coma has a high mortality rate in the United States. Hypothermia, bradycardia, hypotension, hyponatremia, hypoglycemia, and multiorgan failure are associated with a worse prognosis. This elderly patient is hypothermic, hypotensive, and obtunded, so care should be escalated to the intensive care unit (Answer E) over the general medical floor (Answers C and D), and she should not be discharged (Answer B).

Given her mental status, intravenous thyroid hormone replacement is preferred over oral administration (Answer B).

1.3. ANSWER: E)

A loading dose of levothyroxine, 200 to 400 mcg, may be given, with lower doses administered for younger or older patients and those with a history of coronary disease or arrhythmia. Thereafter, a daily replacement dosage should be given (1.6 mcg/kg body weight), reduced to about 75%, as long as it is administered intravenously. Oral therapy, or other enteral therapy if the oral route cannot be used, can be instituted after the patient improves clinically. In addition to aggressive thyroid hormone replacement, empiric glucocorticoid therapy at stress doses should be initiated at the start of therapy for myxedema coma (thus, Answer E is correct and Answer A is incorrect). Intravenous liothyronine, not oral liothyronine (Answer C), can be given in addition to levothyroxine. High doses should be avoided given the association of mortality with high serum T4 during treatment.

1.4. ANSWER: E)

A loading dose of 5-20 mcg can be administered, followed by a maintenance dosage of 2.5-10 mcg every 8 hours, with lower dosages for younger or older patients and those with a history of coronary artery disease or arrhythmia.

Educational Objective:

Identify myxedema coma as an endocrine emergency and devise an initial treatment approach.

2.1. A 30-year-old ♀ presents with tremor and unintentional weight loss of 9 kg over the last 6 months. She has no current pregnancy plans and does not smoke cigarettes.

Exam: Pulse: 120 beats/min. She has moderate proptosis, a diffuse goiter with bruit, and moderate tremor.

Lab: TSH <0.1 mIU/L (0.5-5). TT3: 466 ng/dL (70-200 ng/dL). FT4: 3 ng/dL (0.8-1.8). TPO antibodies 594 IU/mL (<2).

Thyroid-stimulating immunoglobulin: 396% (120% of basal activity). Urine pregnancy test, negative. Baseline liver function test, normal. White blood cell count, normal. She is started on Methimazole, 30 mg/day, and propranolol. Her symptoms improve after a few weeks, but she then develops fever and sore throat Which of the following is the best next step in this patient's management?

A. Continue methimazole and check differential white blood cell count
B. Continue methimazole and test for influenza, Streptococcus, and COVID-19
C. Discontinue methimazole and check differential white blood cell count
D. Discontinue methimazole and refer for thyroidectomy
E. Switch to propylthiouracil and closely follow absolute neutrophil count

2.2. ANSWER: C) Discontinue methimazole and check the differential white blood cell count cell count: This patient most likely developed agranulocytosis due to antithyroid drug therapy, which, when suspected, should prompt immediate treatment cessation and be confirmed by assessing the complete white blood cell count with differential (thus, Answer C is correct and Answers A and B are incorrect). Her normal pretreatment white blood cell count at baseline should not be considered reassuring because this disorder can develop rapidly and unpredictably. A recent large review of agranulocytosis cases in Japan showed that more than half occur within 2 weeks of a previously normal granulocyte count. Therefore, patients receiving antithyroid drugs should be reminded at each clinical interaction of the need to seek medical attention immediately for fever or sore throat, for the explicit purpose of excluding this rare complication, which affects approximately 1 in 200 patients treated.

2.3. ANSWER: C)

A recent study suggests that there may be a genetic predisposition to thionamide-induced agranulocytosis Several HLA haplotypes were shown to increase the risk of agranulocytosis during treatment with methimazole and propylthiouracil, with certain haplotypes being more specific to methimazole-induced agranulocytosis.

After a diagnosis of antithyroid drug-related agranulocytosis, patients should not receive any form of thionamide therapy again. Thus, switching to propylthiouracil (Answer E) is incorrect.

Stopping methimazole and referring for thyroidectomy (Answer D) is incorrect because it does not assess complete blood cell count with differential. After addressing the agranulocytosis, definitive therapy with surgery or radioactive iodine should be pursued to manage the hyperthyroidism.

2.4. ANSWER: C)

Thionamide antithyroid drugs are associated with other important minor and major adverse effects. The most common minor adverse effect is a pruritic rash that affects 3% to 5% of treated patients. This may require antihistamines or switching to an alternative antithyroid drug. In addition to agranulocytosis, major adverse effects include hepatotoxicity and antineutrophil cytoplasmic antibody-positive vasculitis (more common with propylthiouracil).

Educational Objective:

Screen for agranulocytosis in a patient being treated with antithyroid drugs.

3.1. A 45-year-old woman is referred by primary 3 care for evaluation of weight gain and fatigue. She is concerned about a weight gain of 4.5 kg over the last 5 years without an overt dietary change. She has unsuccessfully tried to lose weight by increasing her exercise. After a traumatic brain injury 20 years ago, she has taken a combined oral contraceptive pill for secondary amenorrhea. She recalls having a "full hormone evaluation" at the time of the brain injury and states that everything was normal. She describes worsening fatigue over the last 5 years, but she is still able to work and socialize. She has no headaches, double vision, blurry vision, or polyuria. She describes having a low mood. There is no exogenous steroid exposure

Exam: Pulse: 56. BMI 31. Thyroid is symmetrical and small. She has periorbital edema and acanthosis nigricans. There is no galactorrhea or abdominal striae.

Lab: TSH 1.5 mIU/L (0.5-5). Serum cortisol (10 AM): 15 µg/dL (5-25). HbA1c: 6.2% (4-5.6%) (44 mmol/mol).

CBC: normal. Which is the best next step to establish this patient's diagnosis?

A. Measure IGF-1
B. Measure leptin
C. Measure serum ACTH and cortisol at 8 AM
D. Measure serum free T.
E. Perform 1-mg dexamethasone-suppression test

3.2. ANSWER: D) Measure serumFT4

This patient likely has central. Hypothyroidism due to her traumatic brain injury. Most cases of hypothyroidism are present within the first year after injury, but the timing or presentation can vary from acute (within days) to more than 40 years later. Having a normal serum TSH value does not rule out central hypothyroidism, and the diagnosis can only be made by measuring serum free T (Answer D).

She has no overt signs or symptoms consistent with Cushing syndrome, so the pretest probability is low, and measuring serum ACTH and cortisol at 8 AM (Answer C) or performing a 1-mg dexamethasone-suppression test (Answer E) is incorrect. Her 10 AM serum cortisol level is normal and not consistent with adrenal insufficiency. Normal serum IGF-1 levels (Answer A) do not rule out adult GH deficiency. Although leptin (Answer B) may have a role in hypothalamic obesity, it is prudent to diagnose Secondary hypothyroidism as a manifestation of hypopituitarism in this patient. For patients with central hypothyroidism, the goal of therapy is to achieve a free T value in the upper half of the reference range.

Educational Objective:

Measure free T and serum TSH to diagnose central hypothyroidism.

4.1. A 75-year-old ♂ with a history of atrial fibrillation presents with a growing, Symptomatic, nontoxic, multinodular goiter. He has large bilateral thyroid nodules that are >4 cm (6 cm on the left and 4.5 cm on the right); these nodules have been sampled several times over the years with benign cytology demonstrated on each FNA biopsy. He has been experiencing progressive compressive symptoms, including hoarseness, dysphagia, and a choking sensation for the last 10 years, but the dysphagia has become very bothersome in the last year. He does not take amiodarone. He has no history of stroke. Upper endoscopy and barium swallow studies were negative for other potential etiologies. He was evaluated by surgical colleagues, and they suggested performing a total thyroidectomy. His cardiologist has cleared him for surgery. He understands that he will need lifelong thyroid hormone replacement after surgery, but he has read that some patients are dissatisfied with their treatment. Exam: weight is 70 kg.
Lab: TSH 3.2 mIU/L (0.5-5). FT4: 1.3 ng/dL (0.8-1.8). Which is the best initial approach to this patient's thyroid hormone therapy after thyroidectomy?

A. Desiccated thyroid extract
B. Levothyroxine, 1.6 mcg/kg per day
C. Levothyroxine, 50 mcg daily, with uptitration slowly to achieve normal serum TSH
D. Levothyroxine plus liothyronine combination therapy
E. Liothyronine, 25 mcg twice daily

4.2. ANSWER: B) Levothyroxine, 1.6 mcg/kg per day

After total thyroidectomy, this patient will have overt primary hypothyroidism requiring full weight-based thyroid hormone replacement (Answer B). Although lower initial dosages (Answer C) can be used for subclinical hypothyroidism in elderly patients or patients with comorbid cardiovascular disease, this strategy would only be reasonable for patients who have some degree of residual endogenous thyroid function. Liothyronine monotherapy (Answer E) would not be appropriate as first-line thyroid hormone therapy in this patient with atrial fibrillation given its short half-life and lack of safety data in this population. Likewise, levothyroxine plus liothyronine combination therapy (Answer D) and desiccated thyroid extract (Answer A) would not be appropriate as first-line thyroid hormone replacement therapy in this patient with atrial fibrillation, as levothyroxine monotherapy has established safety and efficacy data in this population. In addition, desiccated thyroid extracts are not FDA-approved and contain supraphysiologic T3 doses (T4/T3 ratio of 4.2). The standard of care for the treatment of hypothyroidism is levothyroxine monotherapy, on which most patients feel well. 15% of patients experience residual symptoms, but levothyroxine monotherapy should be used as the initial treatment approach in this patient

Educational Objective: Devise an initial thyroid hormone replacement regimen for a patient after total thyroidectomy.

5.1. A 40-year-old ♀ with no remarkable medical history is evaluated in the emergency department after sustaining a wrist fracture when she slipped and fell in the snow. She takes no medications or supplements. She works as a teacher but is also the primary caregiver for her mother, who has dementia and thyroid disease. The patient attributes fatigue to working full-time and her caregiving role.

Exam: Pulse: 120. Patellar deep tendon reflexes are brisk. Thyroid: nonpalpable. No thyroid bruit and no proptosis. Thyroid function tests are ordered.

Which is the most likely pattern of thyroid function test results in this patient?

Answer	TSH: 0.5-5 mIU/L	FT4: 0.8-1.8 ng/dL	TT3: 70-200 ng/dL	Thyroglobulin 3-42 ng/mL
A	10 mIU/L	0.6 ng/dL	80 ng/dL	25 ng/dL
B	8 mIU/L	2.1 ng/dL	200 ng/dL	80ng/mL
C	0.01 mIU/L	2.5 ng/dL	180 ng/dL	4 ng/mL
D	0.1 mIU/L	14 ng/dL	290 ng/dL	60 ng/mL
E	2.5 Miu/L	1.1 ng/dL	90 ng/dL	39 ng/mL

5.2. ANSWER: C) TSH: 0.01 mIU/L; FT4: 2.5 ng/dL; TT3 180 ng/dL; thyroglobulin, 4 ng/mL

Answers A and E are incorrect as they illustrate hypothyroid and euthyroid thyroid function profiles, respectively, and are not consistent with this patient's signs and symptoms of thyrotoxicosis. Answer B, with elevated TSH, represents central or TSH-driven hyperthyroidism, which is inconsistent with the history provided.

Answers C and D both describe thyrotoxicosis. In Answer D, the thyroid hormone profile is consistent with hyperthyroidism due to Graves' disease or toxic nodular disease in which the serum T, elevation is more substantial. In some cases, serum T, may, in fact, be the only elevated thyroid hormone. However, this patient does not have a goiter or other clinical stigmata of Graves' disease. She reports struggling with fatigue and has access to her mother's thyroid medication, which is likely to be levothyroxine. Levothyroxine is one of the most commonly prescribed drugs in the world. Chronic suppression of the thyroid gland with levothyroxine in factitious thyrotoxicosis results in low thyroglobulin, as seen in Answer C, and this is the most likely diagnosis.

Educations Objective: Identify the biochemical features of factitious thyrotoxicosis.

6.1. A previously healthy 50-year-old ♂ presents to the emergency department with a 5-month history of progressive abdominal distension, unintentional weight loss of 4 kg, and a 2-day history of jaundice.
Exam: T°: 37°C. Pulse: 48. BP: 110/60. Slight goiter is present.
His abdomen is distended. Sclerae are icteric. Abdominal CT with contrast demonstrates a large gastric tumor with multiple liver lesions suspicious for metastases. Endoscopic biopsy of the Gastric mass confirms a gastrointestinal stromal tumor, and targeted therapy is planned.
Lab: TSH 146 mIU/L (0.5-5). FT4: 0.2 ng/dL (0.8-1.8). TT3: 38 ng/dL (70-200). TPO antibodies: -ve. Which is this patient's most likely diagnosis?

A. Consumptive hypothyroidism
B. Hypothyroidism due to iodinated contrast
C. Nephrotic syndrome
D. Secondary hypothyroidism
E. Thyroid hormone resistance

6.2. ANSWER: A) Consumptive: Gastrointestinal stromal tumors (GISTs) and hepatic vascular tumors have been described to cause the rare paraneoplastic syndrome known as consumptive hypothyroidism (Answer A). Consumptive hypothyroidism is caused by marked overexpression of the thyroid hormone-inactivating enzyme type 3 iodothyronine deiodinase (D3) within the tumor. Increased monitoring is warranted, and affected patients may require supranormal thyroid hormone supplementation. Secondary hypothyroidism (Answer D) is incorrect because the serum TSH is appropriately elevated. Nephrotic syndrome (Answer C) can cause hypothyroidism due to urinary losses of thyroid-binding globulin and bound thyroid hormones, but the patient described in this vignette has a GIST, which is the more likely etiology. Iodinated contrast (Answer B) can cause hypothyroidism via the Wolff-Chaikoff effect, but the more likely etiology in this vignette is the GIST. In thyroid hormone resistance (Answer E), serum TSH is normal or slightly elevated, and thyroid hormone levels are elevated, not low.

Educational Objective:

Identify consumptive hypothyroidism as a rare paraneoplastic syndrome associated with gastrointestinal stromal tumors and hepatic vascular tumors.

7.1. A 34-year-old ♀ presents to an obstetrician after a positive home pregnancy test. She is confirmed to be 8 weeks pregnant. Graves' disease was diagnosed at age 14, at which time she was treated with radioactive iodine ablation followed by levothyroxine replacement therapy. Her current levothyroxine dosage is 125 mcg/day. She has a history of non-adherence to her treatment regimen and has discontinued Levothyroxine completely on previous occasions, citing anxiety, depression, and palpitations as the reasons. Previous cardiac evaluations have not revealed any underlying pathology. The patient has not tolerated medications for anxiety and depression.
Lab: (4 years ago, when she had stopped taking her levothyroxine): TSH: 119 mIU/L (0.5-5). FT4: 0.52 ng/dL (0.8-1.8). When adherence to Levothyroxine 125 mcg/day, was re-established, TSH: 4.5 mIU/L. Current lab: TSH: 257 mIU/L. FT4: 0.35 ng/Dl. She states that she has not been taking levothyroxine for an unclear length of time because of anxiety and palpitations.
Assuming close monitoring to filter her dose, which of the following is the best approach to restarting this patient's thyroid hormone?

A. 50% of her previous levothyroxine dosage of 125 mcg daily
B. Levothyroxine, 112 mcg daily
C. Levothyroxine, 125 mcg daily
D. Levothyroxine, 125 mcg daily, plus liothyronine, 5 mcg daily
E. Levothyroxine, 150 mcg daily

7.2. ANSWER: E) Levothyroxine, 150 mcg daily

There are two issues to consider in treating this patient's hypothyroidism. One is restoring euthyroidism in the setting of severe hypothyroidism. The other is promptly restoring euthyroidism during the first trimester of pregnancy, a time when optimal fetal development requires transplacental transfer of maternal thyroid hormone. As the patient is 8 weeks pregnant, rendering her euthyroid requires a higher dosage of thyroid hormone than would be needed in the nonpregnant state. Most patients with hypothyroidism who are euthyroid before pregnancy They require a 30% increase in their levothyroxine dosage. This is particularly true in individuals with little residual endogenous thyroid function, as may be the case in this patient who was treated with [unclear - possibly "I to ablate her previously overactive thyroid"]..

7.3. ANSWER: E) Levothyroxine, 150 mcg daily

The increased levothyroxine requirement during pregnancy is due to factors such as increased levels of thyroxine-binding globulin and increased blood volume during pregnancy. The best recommendation is to restart levothyroxine at 150 mcg daily (Answer E). Restoring euthyroidism in this patient is a matter of urgency. Inadequately treated hypothyroidism in the first trimester is associated with impaired fetal neurodevelopment, including a reduced intelligence quotient. Hypothyroidism later in pregnancy can be associated with preeclampsia, placental abruption, low birth weight, and fetal death. Despite this patient's severe hypothyroidism, cautious initiation of thyroid hormone should not be the strategy. She is relatively young, does not appear to have cardiac pathology (despite her previous symptoms associated with thyroid hormone treatment), and the full treatment dosage of levothyroxine is imperative for optimizing fetal and pregnancy outcomes.

7.4. ANSWER: E) Levothyroxine, 150 mcg daily

Although not documented and tested as a potential approach, it may also be reasonable to provide this patient with several days of a loading dose of levothyroxine (e.g., twice her anticipated dose) to facilitate a more rapid trajectory toward euthyroidism Treating her with a lower levothyroxine dosage than what rendered her euthyroid in the nonpregnant state (63 mcg [Answer A] and 112 mcg [Answer B]) would be inadequate. These options also do not account for the higher dosage of levothyroxine needed to sustain euthyroidism during pregnancy. Similarly, the dosage of 125 mcg daily (Answer C) is also insufficient now, even though it normalized her TSH value when she was not pregnant. Liothyronine (Answer D) does not cross the placenta. Therefore, combination therapy with both levothyroxine and liothyronine is not recommended during pregnancy because this may result in inadequate provision of thyroid hormone to the fetus.

Educational Objective:

Promptly restore euthyroidism during pregnancy while accounting for the increased thyroid hormone requirement in early pregnancy.

8.1. A 30-year-old ♀ has been newly diagnosed with hyperthyroidism due to Graves' disease and has opted to start MMI 30 mg/day. She has no evidence of orbitopathy. She and her husband are planning their first pregnancy within the next 1-2 years, and she is very concerned about the risks that Graves' disease will pose to a fetus. Her menstrual cycles have been irregular since the onset of hyperthyroid symptoms, and she has no other relevant medical history. Which is the best strategy to reduce the risk of fetal malformations in this scenario?

A. Change from MMI to PTU as soon as pregnancy is diagnosed
B. Change from MMI to PTU before conception
C. Decrease the MMI dosage to the lowest possible to maintain FT4, just above the upper normal limit, once pregnancy is diagnosed
D. Recommend "block-and-replace" therapy with both an antithyroid drug and Levothyroxine
E. Recommend radioactive iodine treatment at least 6 months before pregnancy with normalization of TSH on levothyroxine before conception.

MMI: Methimazole
PTU: Propylthiouracil

8.2. ANSWER: E) Recommend radioactive iodine treatment at least 6 months before pregnancy with normalization of TSH on levothyroxine before conception

Preconception counseling is very important for women with hyperthyroidism due to Graves' disease. Counseling should include a discussion of the risks and benefits of all treatment options and the patient's desired conception timeline. All of the listed approaches could be appropriate in individual patients, depending on the circumstances and the severity of hyperthyroidism. The safety and effectiveness of these approaches have not been directly compared in studies to date.

Methimazole use in pregnancy is associated with a syndrome of fetal anomalies, including dysmorphic facies, choanal or esophageal atresia, abdominal wall defects (e.g., umbilical abnormalities), eye defects, urinary system defects, ventricular septal defects, and aplasia cutis.

8.3. ANSWER: E) Recent studies have shown that these complications are more common than previously thought, affecting 2% to 4% of fetuses exposed to methimazole in early pregnancy, especially during gestational weeks 6 through 10

Propylthiouracil was not previously considered teratogenic. However, a recent Danish study demonstrated that 2% to 3% of children exposed to propylthiouracil in the uterus developed defects, including face cysts, neck cysts, and urinary tract abnormalities (in boys). Although propylthiouracil-Associated birth defects appear to be less severe than methimazole-associated birth defects, but they are not negligible. If antithyroid drugs are continued until pregnancy is diagnosed, there is still some first-trimester exposure. Infants of women who are switched from methimazole to propylthiouracil during the first trimester (Answer A) are at risk for both types of birth defects.

8.4. ANSWER: E)

Radioactive iodine treatment at least 6 months before pregnancy with normalization of TSH on levothyroxine before conception (Answer E) is the only listed approach that would not involve any antithyroid drug exposure in pregnancy. Thus, this strategy is associated with a lower risk of fetal malformations than the other choices (Answers A, B, and C). Women who undergo thyroidectomy or radioactive iodine ablation before conception can still have detectable thyroid receptor-stimulating antibodies, which could pose a risk for fetal and neonatal hyperthyroidism.

A "block-and-replace" strategy (Answer D)

Involves using a higher dosage of an antithyroid drug to render the patient hypothyroid and then treating with levothyroxine to restore euthyroidism.

8.5. ANSWER: E)

This has been suggested as a management strategy that may increase remission rates of Graves' disease or make Graves' disease easier to control. However, this approach is generally not favored because it exposes the patient to a higher dosage of the antithyroid drug and probably does not increase the likelihood of remission. In the case of an individual planning pregnancy, it does not reduce exposure to antithyroid drugs, so it would not reduce the risk of fetal malformations.

Educational Objective:

Counsel women about the teratogenic risks of antithyroid drugs in the first trimester.

9.1. An 87-year-old ♂ with refractory atrial fibrillation is prescribed amiodarone. Three months later, he reports increasing palpitations and diaphoresis

Exam: Pulse: 90 and regular, thyroid is normal size and nontender. He has a fine tremor.

Which would be the most specific indicator of thyrotoxicosis in this patient?

A. Clinical signs and symptoms
B. Elevated FT4.
C. Elevated total T4.
D. Low radioactive iodine uptake
E. Suppressed serum TSH

9.2. ANSWER: E) Suppressed serum TSH. Drug-induced thyrotoxicosis, which occurs: in up to 5% of patients treated with amiodarone, can present both diagnostic and therapeutic challenges The diagnostic uncertainty stems from the dramatic effects amiodarone has on thyroid function, even in previously euthyroid patients. A large iodine load is delivered with each dose (74 mg total iodine, 7.4 mg free iodine per 200 mg tablet). Furthermore, amiodarone inhibits both peripheral and central (intrapituitary) conversion of T4 to T4 through its action on type 1 (DIO1) and type 2 (DIO2) deiodinase enzymes, respectively. Amiodarone also has T4 antagonistic effects at the nuclear level. The common pattern seen in euthyroid patients is high free T4, high total T4, low-normal T4, and high-normal TSH. Because of the potent inhibition of DIO2 and DIO1, either a suppressed TSH level or an elevated (rather than low) T4 level is suggestive of amiodarone-induced thyrotoxicosis.

9.3. ANSWER: E)

An undetectable TSH value in this patient (Answer E) would be the most accurate indicator of thyrotoxicosis.

Elevated total T (Answer C) or free T (Answer B), as noted, can occur in euthyroid individuals. The degree of elevation of total T and free T in an individual who remains euthyroid on amiodarone is greater with the acute effects of amiodarone, which typically occur in the first three months of treatment (approximately a 50% elevation). After three months, the chronic effect of amiodarone results in a 20% to 40% elevation in these hormones. Thus, neither total T nor free T is specific for the detection of amiodarone-induced hyperthyroidism. The free T level should be higher than expected in the setting of thyrotoxicosis (in the mid- to high-normal range), but this is not as helpful as undetectable TSH.

9.4. ANSWER: E)

Radioactive iodine uptake (Answer D) is expected to be lower than normal, even in a euthyroid patient on amiodarone, because of the large iodine load. Clinical signs and symptoms (Answer A) are insufficiently specific to make this diagnosis.

Educational Objective:

Identify the pattern of thyroid function test results in patients with amiodarone-induced thyrotoxicosis.

10.1. A 19-year-old college student was diagnosed with hyperthyroidism due to Graves' disease six months ago. He was prescribed methimazole and referred to endocrinology by his primary care provider, but he has been poorly adhering to treatment and surveillance recommendations. He seeks evaluation because he has been experiencing intermittent inability to move his legs for the last three months. These episodes usually occur after volleyball practice. Each episode has resolved spontaneously within one to two hours. His last episode was one week ago. He has lost 4.5 kg in the past six months. Exam: Pulse: 110, slight goiter + fine tremor, deep tendon reflexes are brisk. Neurologic exam: normal.
Lab: TSH: < 0.01 mIU/L (0.5-5). FT4: 2.5 ng/dL (0.8-1.8). K: 3.5 mEq/L (3.5-5). Ca: 9.5 mg/dL (8.2-10.2). Albumin: 4.1 g/dL (3.5-5). Mg: 2.2 mg/dL (1.5-2.3). Which should be initiated as the most rapid means to prevent additional episodes?

A. Daily potassium supplement
B. Intense home exercise program
C. Methimazole
D. Propranolol
E. Pyridostigmine

10.2. ANSWER: D) Propranolol occurs

This patient has symptoms consistent with a history of thyrotoxic periodic paralysis. Both thyrotoxic and familial varieties of periodic paralysis are caused by an intermittent intracellular shift of potassium, resulting in ineffective sarcolemmal activity within muscle fibrils. The severity of attacks is linked to the severity of hypokalemia. Serum potassium levels return to normal between episodes—hence the normal level in this patient at the time of testing. Attacks may be precipitated by ingestion of large carbohydrate loads or intense physical exertion followed by a period of rest during which paralysis occurs. While alterations in specific genes have been implicated in the familial varieties of periodic paralysis, the nature of the genetic predisposition for the thyrotoxic variety remains unclear. The predominance in Asian males suggests an X-linked abnormality with additional ethnicity-specific genetic influences.

10.3. ANSWER: D) Propranolol occurs: Thyroid hormone and adrenergic stimulation are known to stimulate the Na-K-ATPase pump, which contributes to intermittent hypokalemia. During an episode, judicious potassium therapy assists with recovery of normal muscle function, but the total dose given should be less than 50 mEq to avoid rebound hyperkalemia. There is no evidence that a daily potassium supplement (Answer A) prevents subsequent attacks because total body potassium stores are normal in these patients. Controlling thyrotoxicosis is important. In fact, attacks stop with restoration of a euthyroid state, but this will take many weeks, so methimazole (Answer C) is incorrect. Propranolol (Answer D) inhibits adrenergic stimulation of the NA-K-ATPase pump and helps rapidly prevent recurrent episodes of periodic paralysis. As noted, vigorous exercise may actually precipitate attacks, so an intense exercise program (Answer B) would not be a useful intervention. Pyridostigmine (Answer E) is used to treat myasthenia gravis, not periodic paralysis.

Educational Objective: Diagnose periodic paralysis and recommend treatment.

11.1. A 70-year-old ♂ feels weak and has a racing heart, anxiety, and weight loss shortly after having COVID-19. One month later, his racing heart worsens, and new-onset atrial fibrillation is diagnosed. He is treated with a beta-adrenergic blocker and anticoagulation. Thyroid function tests document hyperthyroidism. Exam: Thyroid: normal-sized, has irregular texture, and is nontender. He has a fine tremor and no proptosis. Thyroid scan and uptake show uptake < 1% at 24 hours. The patient states he has not received Amiodarone or IV contrast. Prednisone is initiated to manage thyroiditis. Over a 3-month period, there is no decline in FT4. Methimazole is added, resulting in only a marginal decrease in FT4. Methimazole is discontinued, and prednisone is continued (table). A single additional evaluation is then performed, which provides information about why the patient's hyperthyroidism had not responded to the therapies that were used. Which of the following is the most likely evaluation that was performed?

A. COVID-19 antibody titer
B. COVID-19 PCR test
C. Serum hCG measurement
D. Spot urine iodine measurement
E. Whole-body iodine scan

	Timeline			
Results	Time of diagnosis of hyperthyroidism	3 months later	4 months later	6 months later
Therapy	None	Prednisone	Prednisone and methimazole	Prednisone
TSH	0..05 mIU/L	0.02 mIU/L	0.01 mIU/L	0.01 mIU/L
FT4	3.5 ng/dL	3.3 ng/dL	2.9 ng/dL	3 ng/dL
TT3	325 ng/dL	295 ng/dL	220 ng/dL	230 ng/dL
TSI	-ve	–	–	–
TRAb	-ve	–	–	–
Thyroglobulin	60 ng/mL	–	–	–
^{123}I Scan	< 1%	–	–	–

11.2. ANSWER: D) Spot urine iodine measurement

This vignette illustrates the differential diagnosis that should be considered when encountering hyperthyroidism associated with low iodine uptake seen on 123I thyroid scan and uptake. Thyroiditis is certainly a potential diagnosis to be considered. The fact that the patient had no neck tenderness makes this less likely, and thyroiditis would have been expected to respond to prednisone
Furthermore, the long duration of hyperthyroidism also makes the diagnosis of thyroiditis less tenable, as the damaged thyroid should not be able to synthesize thyroid hormone for a period of several months. Testing for COVID-19 infection (Answer B) or antibodies to COVID-19 (Answer A) is unlikely to be helpful because thyroiditis associated with COVID-19 infection or vaccination generally responds to steroid therapy and is self-limited in duration.

11.3. ANSWER: D) Spot urine iodine measurement

If thyroiditis is ruled out, remaining considerations are an exogenous iodine load and exogenous thyroid hormone consumption. Exogenous thyroid hormone consumption is unlikely because the patient's thyroglobulin concentration is 60 ng/mL. A random urinary iodine measurement (Answer D) was, in fact, revealing in this patient's case, with an elevated value of 1000 µg/dL. The patient did not provide a history of amiodarone use or iodinated contrast exposure, but further investigation revealed that he was taking nasal drops for sinusitis, which, at the dosage he was using, were believed to provide 12 mg of iodine daily. With cessation of the nasal drops and reinstitution of methimazole, the patient's hyperthyroidism, which was thought to be due to toxic multinodular goiter, gradually resolved.

11.4. ANSWER: D) Spot urine iodine measurement

A whole-body iodine scan (Answer E) is usually performed to rule out struma ovarii in which there are functional thyroid components in a teratoma or dermoid tumor in the ovary.

hCG-induced thyrotoxicosis can be caused by a variety of germ-cell tumors that produce sufficiently high hCG levels to stimulate thyroid hormone production by thyroid tissue. In this setting, uptake would be anticipated to be elevated when thyroid scan and uptake are performed. Therefore, this could not provide a single diagnosis in this patient, as an iodine load would have to be present concomitantly to account for the low uptake seen on thyroid scan and uptake.

Measuring serum hCG (Answer C) is incorrect.

Educational Objective:

Differentiate among the potential causes of hyperthyroidism in the setting of low uptake documented with a thyroid scan and uptake.

12.1. A 75-year-old ♀ presents with a 1-year history of signs and symptoms suggestive of thyrotoxicosis, including weight loss and palpitations. Exam: 3-cm, right-sided thyroid nodule is palpated, and a tremor of her outstretched hands is noted. There is no proptosis. Biochemical evaluation confirms hyperthyroidism. A diagnostic ^{125}I thyroid scan is performed (see image). Which is the most likely etiology of the patient's thyrotoxicosis?

A. Activating variant in the gene encoding the sodium-iodide symporter
B. Germline activating variant in the gene encoding the TSH receptor
C. Inactivating variant in the gene encoding the Ga subunit
D. Somatic activating variant in the gene encoding the TSH receptor
E. Thyroid hemiagenesis and Graves' disease

12.2. ANSWER: D) Somatic activating variant in the gene encoding the TSH receptor

The thyroid scan shows a large, right-sided autonomous thyroid nodule with suppression of the left lobe, which is only faintly visible in the image. This can be described as a "toxic" or "hot" adenoma/nodule. Most such nodules have somatic activating variants in the genes encoding the TSH receptor (Answer D) or the G,a subunit, leading to constitutive activation and hyperfunction within the nodule. When an autonomous nodule grows to a large enough mass (classically described as 3 cm or more in maximum diameter), overt hyperthyroidism may occur, as in this patient. Because TSH becomes suppressed in the face of elevated thyroid hormone values, the activity of the contralateral lobe is suppressed.

12.3. ANSWER: D) In addition to somatic variants affecting only the "hot" thyroid nodule, as described in this case, germline pathogenic variants can also occur in the gene encoding the TSH receptor (Answer B) that would affect the entire thyroid and all other cells of the body. This leads to an inherited form of thyrotoxicosis that presents with diffuse thyrotoxicosis evident in infancy or later in life as nonautoimmune thyrotoxicosis with a diffuse goiter and increased radioactive iodine uptake throughout the thyroid gland. This is not the case in this vignette. Activating variants in the gene encoding the sodium-iodide symporter (Answer A) have not been reported as a source of thyroid autonomy. Inactivating variants in the gene encoding the Gα subunit (Answer C) would not lead to enhanced hormonogenesis. Hemiagenesis (Answer E) is excluded by the thyroid scan image showing bilateral thyroid tissue

Educational Objective: Identify common patterns on thyroid scans and describe the pathogenesis of a solitary hot nodule.

13.1. A 25-year-old ♀ found TSH 0.18 mIU/L routine exam. No thyrotoxic symptoms. She is otherwise healthy and is not currently taking any medications or supplements. Exam: small goiter. No bruit or palpable nodules. No signs of thyroid eye disease. Pulse: 78.
Lab 4 months later: TSH: 0.19 mIU/L (0.5-5). FT4: 1.6 ng/dL (0.8-1.8). TT3: 166 ng/dL (70-200). Thyroid-stimulating immunoglobulin: 137% (≤120% of basal activity). She has 2 children and is not planning additional pregnancies. She has a copper intrauterine device.
Which is the best next step in this patient's management?

A. Repeat thyroid function tests in 3 to 6 months
B. Schedule radioactive iodine treatment
C. Schedule thyroid ultrasonography
D. Start atenolol, 25 mg daily
E. Start methimazole, 5 mg daily

13.2. ANSWER: A) Repeat thyroid function tests in 3 to 6 months

Subclinical hyperthyroidism, in which serum TSH values are low but thyroid hormone levels remain normal, is relatively common, affecting approximately 1.5% of the US adult population. Approximately 5% of patients progress to overt hyperthyroidism, an outcome that is more likely when TSH is fully suppressed. Up to one-third of patients with subclinical hyperthyroidism spontaneously become euthyroid again. This phenomenon is most common when the underlying cause of their hyperthyroidism is Graves' disease and when the baseline TSH concentration is between 0.1-0.4 mIU/L. Subclinical hyperthyroidism is associated with an increased risk of all-cause and cardiovascular mortality, atrial fibrillation, osteoporosis, and fracture. However, there is currently limited evidence for treatment benefit, particularly in younger individuals, and treatment itself confers some risks.

13.3. ANSWER: A) Repeat thyroid function tests in 3 to 6 months

Current guidelines recommend observation with monitoring of thyroid function (Answer A) rather than treatment (Answers B and E) for asymptomatic patients younger than 65 years who do not have cardiac disease or osteoporosis in whose TSH concentrations are persistently lower than normal but 0.1 mIU/L or greater. B-Adrenergic blockade (Answer D) might be useful in the setting of hyperthyroid symptoms or tachycardia, but this patient has neither Thyroid/US (Answer C) is not necessary at this point, given the relatively unremarkable thyroid examination. If performed, US might show increased vascularity of the thyroid gland, suggestive of Graves' disease. However, Graves' disease is already evident based on the elevated thyroid-stimulating immunoglobulin value.

Educational Objective:

List indications for treatment of subclinical hyperthyroidism.

14.1. A 60-year-old ♀ with a history of 14 post-ablative hypothyroidism presents for initial consultation. She has been taking Levothyroxine 125 mcg/day, for the past 10 years with excellent adherence and stable thyroid hormone levels. However, she describes continued fatigue and "brain fog" and is frustrated by her inability to lose weight. Despite adherence to dietary and exercise recommendations, her weight has increased 4 kg over the past 2 years.

Exam: BP: 132/76. Weight: 77 kg. Thyroid: firm, mobile, 15 g size. The relaxation phase of her deep tendon reflexes is normal.

Lab: TSH 2.59 mIU/L (0.5-5). FT4: 1.6 ng/dL (0.8-1.8).

She would like to increase her Levothyroxine dosage to a goal TSH in the low-normal range (0.5-0.8 mIU/L), which she believes will help her lose weight and improve her quality of life. Which would be most likely if this patient's Levothyroxine dosage were increased as she has requested?

A. Decreased visceral fat mass
B. Improved cognitive function
C. Improved mood
D. Increased resting energy expenditure
E. Perceived benefit of the change

14.2. ANSWER: E) Perceived benefit of the change

About 10% to 15% of levothyroxine-treated patients with hypothyroidism report feeling unwell despite having normal serum TSH values. In patients with overt hypothyroidism, initiation of levothyroxine therapy is associated with modest weight loss that tends to be transient and is most likely due to diuresis rather than to changes in fat mass. Patients often anticipate that a levothyroxine dosage that results in lower TSH levels within the normal range may assist with weight loss or Otherwise, improve quality of life. A randomized controlled trial has demonstrated that patients were unable to detect differences in the symptoms associated with hypothyroidism when the levothyroxine dosage was changed by approximately 20%.

14.3. ANSWER: E) Perceived benefit of the change

More recently, another randomized clinical trial that examined the effects of TSH variation within or just above the normal range in levothyroxine-treated patients concluded that body composition (including visceral and total fat [Answer B]), resting energy expenditure [Answer D], total energy expenditure, thermic effect of food, physical activity energy expenditure, and daily energy intake did not vary by treatment group. The same trial did not report any differences in quality of life, mood [Answer C], or cognition [Answer B] based on the target TSH group. Interestingly, although trial participants were blinded to their treatment and unable to accurately determine how their levothyroxine dosages had been adjusted, they preferred levothyroxine dosages they perceived to be higher.

14.4. ANSWER: E) Perceived benefit of the change

Thus, levothyroxine-treated patients may prefer perceived higher levothyroxine dosages [Answer E] despite a lack of objective benefit. Current guidelines simply recommend targeting a serum TSH value within the reference range in levothyroxine-treated patients and note that additional research is needed to determine whether It is useful to adjust the levothyroxine dosage to influence the TSH concentration within the goal reference range for residual signs and symptoms of hypothyroidism.

Educational Objective:

Counsel patients about anticipated clinical outcomes when the levothyroxine dosage is adjusted to achieve TSH values within the reference range.

15.1. A 64-year-old ♀has been treated for primary hypothyroidism for several decades. While taking a Levothyroxine dosage of 112 mcg /day, her records show that she has maintained a stable TSH: 1-3 mIU/L. She is hospitalized for abdominal pain, and an aortic aneurysm is diagnosed. During recovery from surgery, continuous enteral tube feeding is initiated. Her hypothyroidism treatment regimen is maintained with Levothyroxine 112 mcg/day (tablet given orally at 6:30 AM). Her Hospitalization is prolonged because she develops pneumonia. She has not had hyperglycemia or received insulin during this hospitalization. Now TSH: 38 mIU/L.
Which would be the most cost-effective change in this patient's therapeutic regimen to normalize serum TSH?

A. Discontinue enteral feeding
B. Hold enteral feeding from 5:30 AM to 7:30 AM daily
C. Increase Levothyroxine dosage to 125 mcg daily
D. Switch Levothyroxine tablets to IV Levothyroxine
E. Switch Levothyroxine tablets to liquid Levothyroxine in a gel capsule

15.2. ANSWER: B) Hold enteral feeding from 5:30 AM to 7:30 AM daily

Each of the listed options would most likely lower this patient's serum TSH. Switching to a liquid levothyroxine formulation (Answer E), switching to intravenous levothyroxine (Answer D), or holding enteral feeding from 5:30 AM to 7:30 AM (Answer B) would all be reasonable approaches to correcting the patient's elevated TSH. Liquid levothyroxine (Answer E), either given directly in liquid form (recently available in the United States) or delivered within a gelatin capsule (available in the United States), has the advantage of improved absorption in several levothyroxine-malabsorptive states, including those associated with proton-pump inhibitors, celiac disease, and coexistent food consumption or coexistent enteral feeding. Although this option is reasonable, it is probably not the most cost-effective, as levothyroxine tablets are generally less expensive than levothyroxine in gel capsules or as a liquid, and tablets are also covered by most Insurance plans.

15.3. ANSWER: B) Hold enteral feeding from 5:30 AM to 7:30 AM daily

Many hospital formulations do not carry the gel capsule or liquid formulations. Switching to intravenous levothyroxine (Answer D) is simple and would be guaranteed to reverse the problem of elevated TSH. The dose of intravenous levothyroxine should be 70% to 80% of the oral dose (78-89 mcg). Single-use vials are available containing either 100 mcg, 200 mcg, or 500 mcg of levothyroxine as a lyophilized powder. Reconstitution using 5 mL of isotonic saline is recommended. Although this option is effective and the dosage of levothyroxine can be readily adjusted based on through levels of free T, and based on TSH values over a longer period, many hospitals discourage its use because it is more expensive than tablet preparations. Some hospitals also require an endocrinology consultation before intravenous levothyroxine can be used.

15.4. ANSWER: B) Hold enteral feeding from 5:30 AM to 7:30 AM daily

In the outpatient setting, a delay of 30 to 60 minutes between levothyroxine administration and food intake is recommended. An even longer separation of up to 4 hours is recommended for calcium and iron. In a 2014 study by Pirola et al., normal serum TSH values were maintained in hospitalized patients receiving enteral tube feeds if the feeds were held for 1 hour to allow for administration of crushed levothyroxine tablets. Temporarily suspending the patient's tube feeding for 1 to 2 hours (Answer B) would encourage better levothyroxine absorption and is the most cost-effective approach. Although this option avoids the cost of intravenous levothyroxine preparations, it is probably not the most convenient choice from the nursing staff's perspective.

15.5. ANSWER: B) Hold enteral feeding from 5:30 AM to 7:30 AM daily

In general, administering levothyroxine in the hospital setting is associated with errors that result in out-of-range TSH values. Elevated TSH values seem to be associated with increased length of hospital stay

Discontinuing enteral feeding (Answer A) might normalize the patient's TSH, but caloric restriction is not in the best interest of a patient requiring a prolonged hospital stay.

Increasing the levothyroxine dosage to 125 mcg daily (Answer C) is incorrect, as the relatively small increase would be insufficient to lower TSH into the normal range.

Educational Objective:

Differentiate among the options available to correct elevated TSH due to reduced levothyroxine absorption in hospitalized patients.

16.1. An 80-year-old ♀ with fatigue and weight gain is referred for evaluation of subclinical hypothyroidism. She gained 4.5 kg since retiring 8 years ago, and she frequently takes a midday nap. Her medical history is notable for hyperlipidemia, which has been managed by diet alone. Exam: normal-sized thyroid. No palpable nodules. The rest of her exam: normal.
Lab: TSH: 7.9 mIU/L (0.5-5). FT4: 1.3 ng/dL (0.8-1.8). LDL: 160 mg/dL (<100). HDL: 38 mg/dL (>60). TPO antibodies: elevated. Which potential effect of initiating levothyroxine treatment for this patient is most strongly supported by current evidence?

A. Iatrogenic subclinical hyperthyroidism
B. Improved cognitive function
C. Increased HDL cholesterol
D. Less fatigue
E. Weight loss

16.2. Hyperthyroidism ANSWER: A) Iatrogenic subclinical

In large studies, subclinical hypothyroidism has been associated with increased cardiovascular risk and subtly increased symptom scores The adverse effects of subclinical hypothyroidism have been most clearly demonstrated when the serum TSH concentration is 10.0 mIU/L or greater. However, very large-scale trials would likely be required to demonstrate benefits, and no intervention trial to date has demonstrated a consistent improvement in sense of well-being or energy level (Answer D), weight reduction (Answer E), or improvement in cognitive function (Answer B) with treatment of subclinical hypothyroidism when the baseline TSH is less than 10.0 mIU/L. While some, but not all, studies have shown decreases in LDL cholesterol following initiation of levothyroxine treatment for subclinical hypothyroidism, HDL (Answer C) is typically not altered in patients with subclinical hypothyroidism.

16.3. Hyperthyroidism ANSWER: A) Iatrogenic subclinical

Current recommendations, in the absence of unequivocal evidence for treatment benefit, are to treat subclinical hypothyroidism when the TSH concentration is consistently greater than 10 mIU/L and to individualize treatment decisions. When the TSH concentration is between 5.0 and 10.0 mIU/L

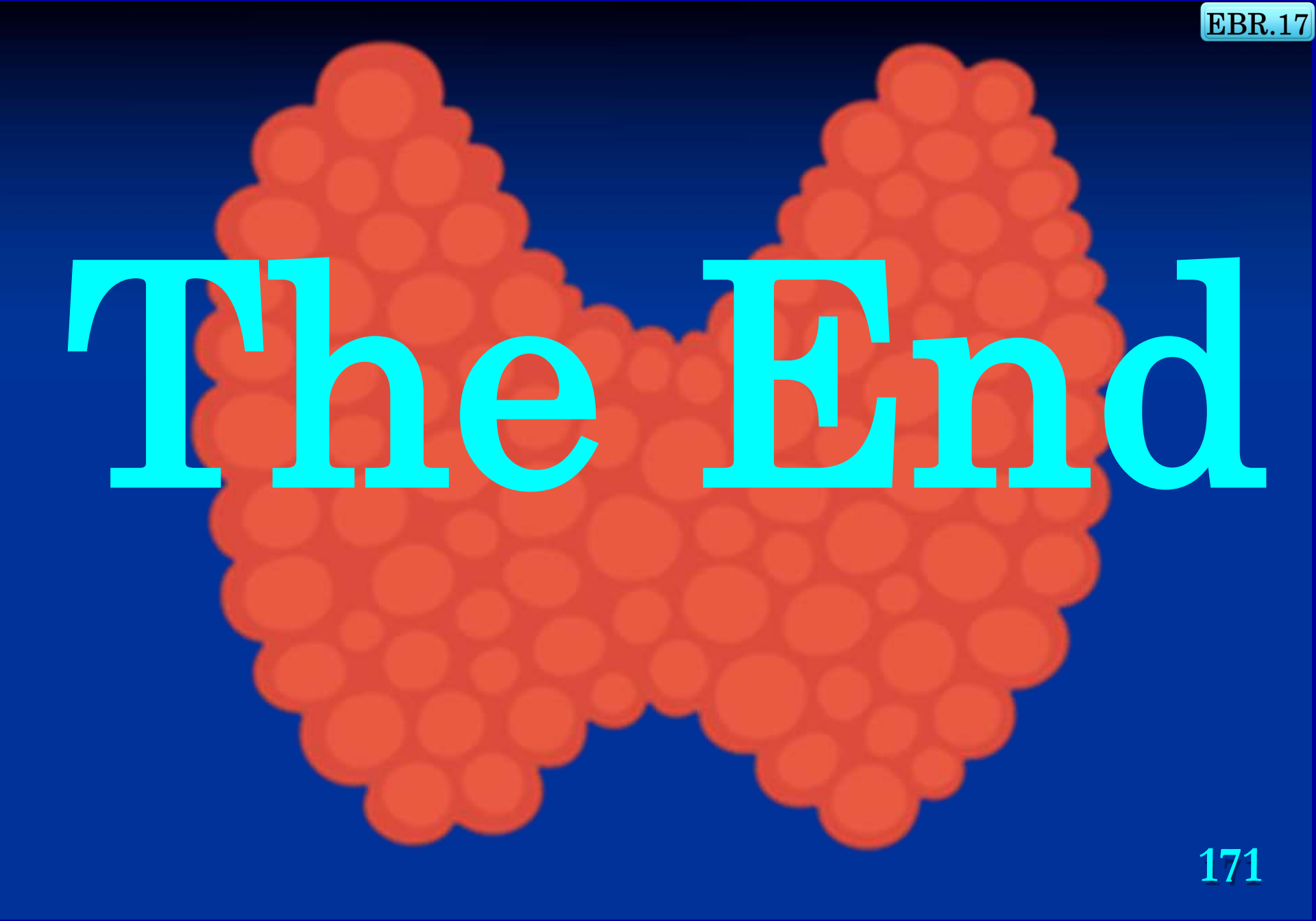
Analysis of the NHANES-III population survey (Third National Health and Nutrition Examination Survey) has shown that normal elderly patients without goiter or serologic evidence of Hashimoto's thyroiditis have a rightward shift in the upper normal limit for TSH, with the upper 95% CI ranging to approximately 7.5 mIU/L in octogenarians. However, this patient's TSH value of 7.9 mIU/L is most likely truly abnormal.

16.4. Hyperthyroidism ANSWER: A) Iatrogenic subclinical

Patients with positive TPO antibodies are at higher risk for overt hypothyroidism and may be good candidates for levothyroxine therapy to prevent this progression. It is important to monitor treatment appropriately because iatrogenic subclinical hyperthyroidism (Answer A) is clearly detrimental, and studies have shown that 14% to 21% of individuals taking levothyroxine are overtreated.

Educational Objective:

Describe the limited evidence for the benefit of levothyroxine initiation when the TSH concentration is less than 10.0 mIU/L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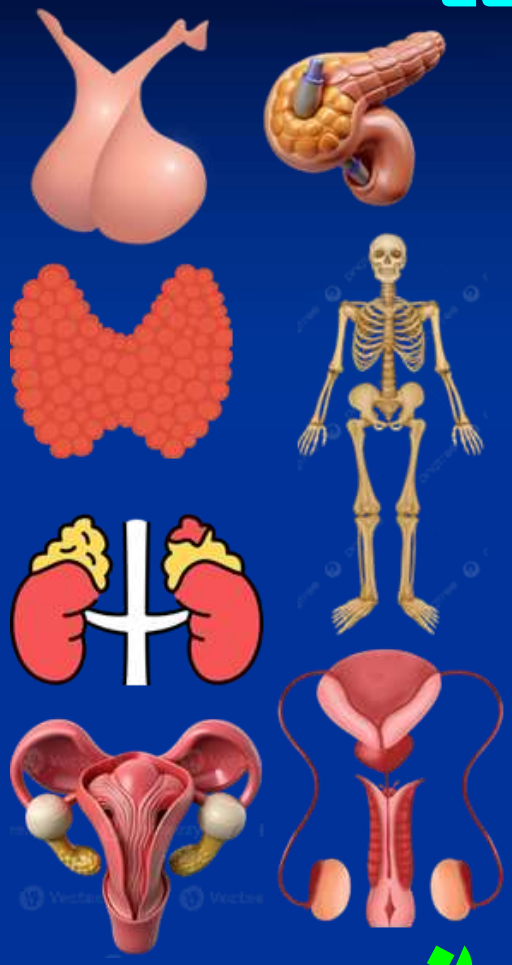

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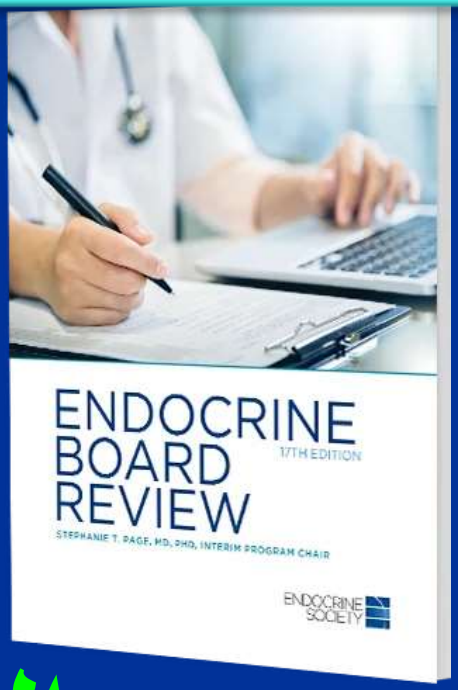

- Adrenals
- Pituitary
- Lipids/ Obesity
- Diabetes
- Reproduction
- Thyroid
- Ca/Bone

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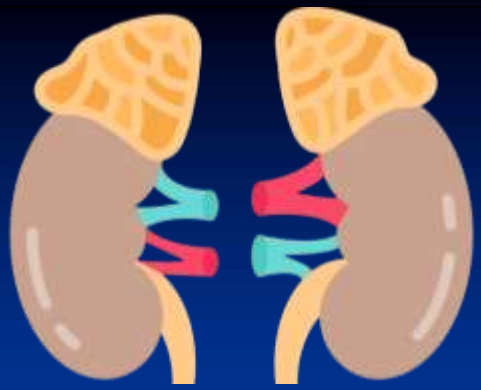

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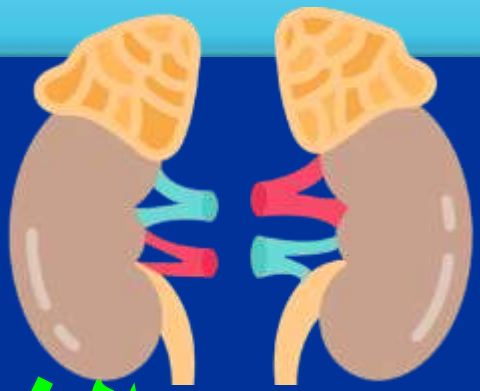

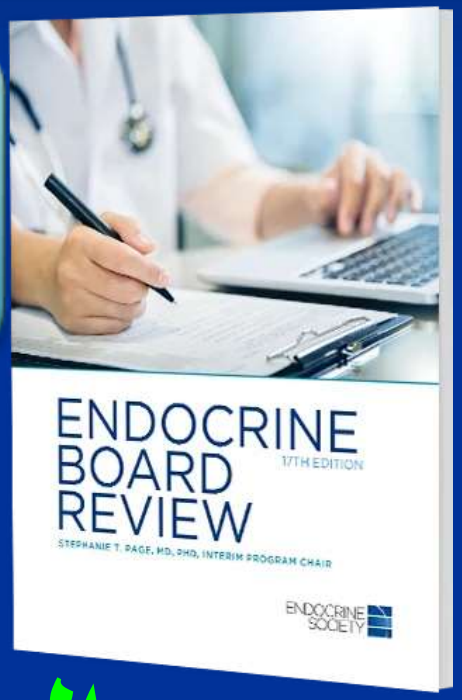

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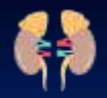


1.1. A 61-year-old ♂ with a history of hypertension has a resectable left carotid body paraganglioma. Genetic testing confirms the presence of a germline succinate dehydrogenase type D (SDHD) pathogenic variant.

His plasma and urinary metanephrines are normal. However, his plasma 3-methoxytyramine levels are elevated.

Exam: BP: 159/64. Pulse: 87.

Medications: Amlodipine: 10 mg/day, Lisinopril 40 mg/day.

Which biogenic amines does this patient's tumor make?

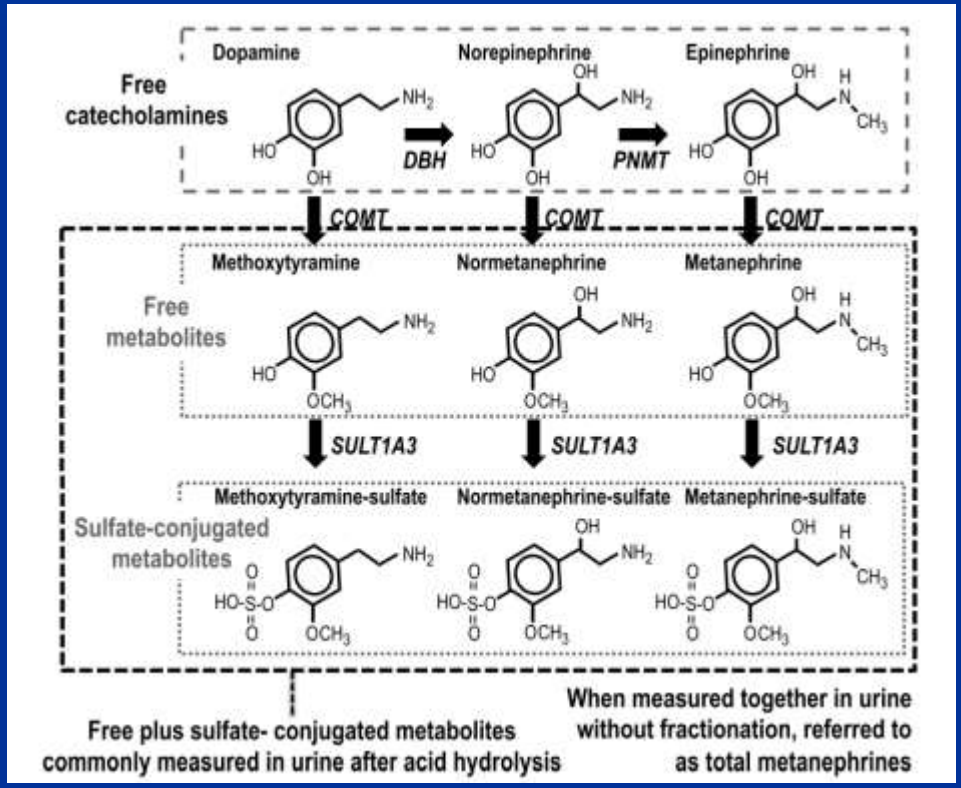
A. Dopamine.
B. Epinephrine
C. Epinephrine + norepinephrine
D. Norepinephrine
E. Serotonin

1.2. ANSWER: A) Dopamine: The standard of care for biochemical testing for pheochromocytoma/paraganglioma is measurement of plasma metanephrines/normetanephrines or 24-hour urinary metanephrines/normetanephrines. Metanephrines/normetanephrines are stable breakdown products of catecholamines, such as epinephrine and norepinephrine In the last several years, work from Eisenhofer and colleagues has demonstrated that the breakdown product of dopamine, 3-methoxytyramine, measured from plasma is helpful in diagnosing patients with dopamine-only producing tumors, especially in patients with head and neck paragangliomas and particularly if related to SDHD pathogenic variants. Since the patient in this vignette has SDHD-associated paraganglioma, it is most likely a dopamine-secreting tumor (Answer A) that would be more accurately diagnosed by documenting elevated plasma 3-methoxytyramine rather than measuring dopamine or 3-methoxytyramine in a 24-hour urine collection. Epinephrine (Answer B) is broken down to metanephrine. Norepinephrine (Answer D) is broken down to normetanephrine (see figure). Serotonin (Answer E) is not measured when evaluating PPGLs.

Educational Objective:

Identify 3-methoxytyramine as a breakdown product of dopamine, whereas metanephrine and normetanephrine are derived from epinephrine and norepinephrine, respectively.

1.3. Schematic diagram to illustrate differences in free vs sulfate conjugated O-methylated catecholamine metabolites and how these many be measured in urine as either the free metabolites or the deconjugated metabolites after an acid hydrolysis step. Commonly measured urinary deconjugated metanephrines represent the combination of free and much larger amounts of sulfate-conjugated metabolites. With spectrophotometric assays all metabolites are measured together as a single value without fractionation (ie, chromatographic separation); hence the term “total” metanephrines in the plural form. While metanephrine (singular) refers to the O-methylated metabolite of epinephrine, normetanephrine refers to the O-methylated metabolite of norepinephrine and metanephrines (plural) refer to both metanephrine and normetanephrine. Note, that similar to norepinephrine and epinephrine, there is no plural form for normetanephrine. Abbreviations: DBH, dopamine beta hydroxylase; COMT, catechol-O-methyltransferase; PNMT, Phenylethanolamine N-methyltransferase; SULT1A3, sulfotransferase type 1A3.



2.1. A 26-year-old ♀ with a history of birth-related polycythemia, diarrhea, and episodes of hypertension presents for evaluation for abdominal paraganglioma. She has no family history of pheochromocytoma/paraganglioma. Germline genetic testing is negative for any known pathogenic variants.

Exam: BP: 145/85. Pulse: 91. Examination findings are normal.

Lab: Plasma normetanephrine = 19,000 pg/mL (<165). Na: 140 mEq/L (136-142 mEq/L). K: 4.2 mEq/L (3.5-5). Ca: 10 mg/dL (8.2-10.2). Cr: 1 mg/dL (0.6-1.1). Hematocrit 70% (35-45%). This patient most likely has a somatic driver variant in which of the following genes?

A. EPASI (endothelial PAS domain protein 1).
B. NF1 (neurofibromin 1)
C. PRKARIA (protein kinase cAMP-dependent type I regulatory subunit alpha)
D. RET (RET proto-oncogene)
E. VHL (von Hippel-Lindau tumor suppressor)

2.2. ANSWER: A) EPASI (endothelial PAS domain protein 1)

Pacak-Zhuang syndrome due to EPASI pathogenic variants (Answer A) was described more than a decade ago, and it is characterized by early-onset (often at birth) polycythemia, duodenal somatostatinoma, and multiple paragangliomas and pheochromocytomas. The somatic driver variant affects hypoxia-inducible factor 2a, encoded by EPASI (formerly known as HIF2A), and it is an activating gene variant that increases erythropoietin. This patient has a history of polycythemia at birth. Her current symptom of diarrhea is likely due to a duodenal somatostatinoma. Her normetanephrine is elevated, which is consistent with the presence of an EPASI variant (see table).

Educational Objective:

Identify key genetic drivers associated with endocrine neoplasias.

2.2. ANSWER: A) EPASI (endothelial PAS domain protein 1)

Gene	Syndrome	Inheritance	Manifestations
EPASI	PPCL-somatostatinoma polycythemia syndrome (Pacok Zhuang syndrome)	Unknown (postzygotic	Polycythemia, somatostatinoma, retinol abnormalities, organ cysts
VHL	von Hippel-Lindau syndrome	Autosomal dominant	Hemangioblastoma, renal cell carcinoma, epididymal cystadenoma, pancreatic neuroendocrine tumors, retinal abnormalities
RET	Multiple endocrine neoplasia type 2	Autosomal dominant	Multiple endocrine neoplasia type 2A: medullary thyroid carcinoma, parathyroid adenoma; multiple endocrine neoplasia type 28: medullary thyroid carcinoma, mucosal neuromuscular dysmorphic features
NF1	Neurofibromatosis type 1	Autosomal dominant	Café-au-lait spots, Lisch nodules in the eye, neurofibromas, intellectual disability, dysmorphic features, skeletal abnormalities
PRKARIA	Comey complex	Autosomal dominant	Primary pigmented nodular adrenocortical disease resulting in Cushing syndrome, acromegaly from pituitary adenoma, gonadal, and thyroid tumors. Other tumors include cardiac myxomas, psammomatous melanotic schwannomas, and breast ductal adenomas.

3.1. A 69-year-old ♂ presents for evaluation of secondary hypertension. He has a history of heart failure with preserved ejection fraction, gastroesophageal reflux disease, T2D, and hyperlipidemia. Hypertension was diagnosed 10 years ago. At a recent visit with a new primary care physician, a secondary workup for hypertension was initiated.
Medications: Lisinopril 5 mg/day; Metoprolol 25 mg/day; Furosemide 20 mg twice/day; Omeprazole 20 mg/day; Atorvastatin 20 mg/day; and Empagliflozin 12.5 mg/day.
Exam: BP: 137/90. Exam findings are normal other than 1+ bilateral lower-extremity edema. Lab: Na: 140 mEq/L (136-142). K: 3.8 mEq/L (3.5-5). Metanephrines: normal. Urinary free cortisol: normal. Aldosterone 11 ng/dL (4-21 ng/dL). Renin <0.6 ng/mL/h (0.6-4.3). Cr: 1.6 mg/dL (0.7-1.3). HbA1c: 6.6% (4-5.6%) (49 mmol/mol [20-38 mmol/mol])
Abdominal CT shows right adrenal medial limb thickening.
Repeated measurements of aldosterone and renin are similar
Which of the following is the best next step in this patient's management?

A. Continue current management plan
B. Perform dexamethasone-suppression test
C. Perform right adrenalectomy
D. Stop furosemide and repeat screening
E. Treat medically with a mineralocorticoid receptor antagonist.

3.2. ANSWER: E) Treat medically with a mineralocorticoid receptor antagonist

This patient's hyperaldosteronism is mild, and his blood pressure is slightly above target. Therefore, a mineralocorticoid receptor antagonist (Answer E) would be the most effective treatment for this elderly man with heart failure and kidney insufficiency. Proceeding to right adrenalectomy (Answer C) without knowing which adrenal is secreting aldosterone (via adrenal vein sampling) would be incorrect. CT does not have good consistency with identifying the location of the aldosterone-producing tumor Stopping furosemide and repeating screening (Answer D) would not be the best next step. As a diuretic, furosemide should raise renin. The renin-angiotensin system is then activated, which can indirectly affect aldosterone levels. The patient's renin is already suppressed, even with furosemide. Therefore, stopping furosemide would not necessarily change management but instead may worsen his heart failure symptoms. His blood pressure is not at target, so simply continuing current management (Answer A) is insufficient. Untreated hyperaldosteronism can lead to stroke, atrial fibrillation, and myocardial infarction This patient has no known adrenal mass or clinical stigmata of hypercortisolism. A dexamethasone-suppression test (Answer B) is unnecessary.

Educational Objective:

Identify which patients will likely benefit from adrenal vein sampling versus medical therapy with a mineralocorticoid receptor antagonist in primary hyperaldosteronism

4.1. 4. A 21-year-old ♀ with classic congenital adrenal hyperplasia (21-hydroxylase deficiency) presents for a follow-up visit. Her hydrocortisone dosage was increased 3 months ago due to concerns about hyperandrogenism. She is currently taking Hydrocortisone at the following times: 20 mg at 7 AM, 15 mg at 3 PM, and 5 mg at bedtime (her previous regimen was 15 mg/10 mg/5 mg). She also takes Fludrocortisone, 0.05 mg/day. BMI: 31 kg/m². Since her last visit, she has gained 9 kg.
Lab: Na 140 mEq/L (136-142). K: 4.6 mEq/L (3.5-5). Cr: 1 mg/dL (0.6-1.1). TSH: 1 mIU/L (0.5-5). 17-Hydroxprogesterone: 9800 ng/dL (< 80 ng/dL [follicular]). Androstenedione: 620 ng/dL (30-200).Which of the following is the best recommendation to help reduce this patient's weight and address her hyperandrogenism?

A. Add Crinecerfont 100 mg twice daily, and reduce hydrocortisone doses to 15 mg/10 mg/5 mg.
B. Add Dexamethasone, 1 mg nightly, and continue the hydrocortisone regimen at 20 mg/15 mg/5 mg
C. Add Prednisolone 10 mg nightly, and reduce hydrocortisone doses to 20 mg/10 mg/5 mg
D. Reduce the hydrocortisone doses to 10 mg/10 mg/5 mg
E. Recommend no change

4.2. ANSWER: A) Add Crinecerfont, 100 mg twice daily, and reduce hydrocortisone doses to 15 mg/10 mg/5 mg

Crinecerfont (Answer A) is a corticotropin-releasing factor type 1 receptor antagonist developed to reduce androstenedione levels. In a phase-3 clinical trial conducted by Auchus et al., 122 patients with classic 21-hydroxylase deficiency were treated with Crinecerfont, and 60 patients were treated with placebo. The primary efficacy in this trial was the percentage change in the daily glucocorticoid dosage from baseline to 24 weeks By the 24th week, daily glucocorticoids were reduced by 27% in the Crinecerfont-treated group compared with 10% in the placebo group. In December 2024, the US FDA approved the use of Crinecerfont as an adjuvant therapy to glucocorticoids for patients with classic congenital hyperplasia who may have elevated androgens.

Although reducing the hydrocortisone doses (Answer D) would help with her weight, it would not address her hyperandrogenism. The addition of dexamethasone (Answer B) or prednisolone (Answer C) would increase her weight. Recommending no change (Answer E) ignores both of the patient's underlying concerns

Educational Objective

Recommend a corticotropin-releasing factor type 1 receptor antagonist as an adjuvant therapy to glucocorticoids for patients with classic congenital adrenal hyperplasia and hyperandrogenism.

5.1. Adrenal vein sampling is being considered for a 38-year-old ♀ with confirmed hyperaldosteronism. Medications: Spironolactone 200 mg twice/day; Amlodipine 10 mg/day; Metoprolol 75 mg twice/day; Doxazosin 16 mg/day; and KCl: 30 mEq twice day. Lab: Serum aldosterone: 43 ng/dL (4-21). Plasma renin activity: < 0.5 ng/mL/h (0.6-4.3). Serum Cr: 1.3 mg/dL (0.6-1.1). Serum K: 3.7 mEq/L (3.5-5). Metanephrines: normal. Dexamethasone-suppression testing results in a cortisol value of 0.5 µg/dL (13.8 nmol/L). CT shows a 1.7-cm right adrenal mass. BP: 157/80. The patient is anxious about a cure and wants to explore all the necessary means of determining whether the source of her hyperaldosteronism can be removed Regarding adrenal vein sampling, which is the best next step in this patient's preparation?

A. Advise medical therapy instead of proceeding with adrenal vein sampling
B. Advise her to eat a high-salt diet
C. Proceed with adrenal vein sampling without stopping Spironolactone.
D. Reduce spironolactone dosage to 50 mg twice daily
E. Stop spironolactone for 4 weeks

5.2. ANSWER: C) Proceed with adrenal vein 5 sampling without stopping spironolactone

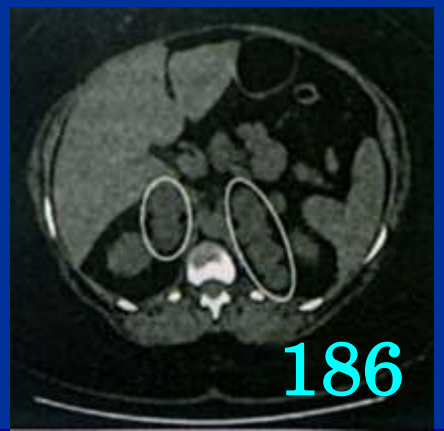
This woman with confirmed hyperaldosteronism would like to proceed with a full workup to determine the etiology of her disease and the most effective treatment. As she has confirmed hyperaldosteronism, proceeding with adrenal vein sampling is reasonable, and there may be a higher likelihood of lateralization and subsequent treatment success with adrenalectomy. Adrenal vein sampling can proceed without stopping spironolactone (Answer C) because her renin is still suppressed with high-dose spironolactone treatment that is still requiring potassium supplementation. Her BP values are not ideal, even with the use of several antihypertensive agents. Several studies have demonstrated successful adrenal vein sampling in patients who continue spironolactone while renin is still suppressed. If Spironolactone is withdrawn (Answer E) or the dosage is reduced (Answer D), controlling her BP would be extremely difficult, and there could be a chance that she may have a cerebrovascular accident with severely elevated BP. The patient is a good candidate for adrenal vein sampling and, more importantly, she would like to proceed with a complete workup, so advising medical therapy instead of adrenal vein sampling (Answer A) is incorrect. A high-salt diet (Answer B) would increase her BP.

Educational Objective:

Advise selected patients with severe hyperaldosteronism who have suppressed renin on mineralocorticoid receptor blockade that they can still undergo adrenal vein sampling.

6.1. A 58-year-old ♀ with a history of hypertension, T2D, asthma, meningioma, and seasonal allergies is referred for adrenal masses incidentally discovered on CT when she presented to the emergency department for abdominal pain (image, circles). Exam: BP: 152/85. Pulse: 90. T°: 36.9°C. She has supraclavicular fat pads, purple striae on her abdomen, and proximal muscle weakness.
Lab: Urinary free cortisol: 150 µg/24 h (4-50). (repeated: 160 µg/24 h). Cortisol values after a dexamethasone-suppression test are 8 µg/dL, 10 µg/dL, and 8 µg/dL. Given the patient's bilateral disease, which genes should be targeted if genetic testing is ordered?

A. ARMC5.
B. BRAF
C. MAX
D. p53
E. RET



6.2. ANSWER: A) ARMCS

In patients with primary bilateral macronodular adrenal hyperplasia, testing for germline pathogenic variants in the ARMCS gene (armadillo repeat containing 5) should be offered (Answer A). Between 20% and 55% of patients with primary bilateral macronodular adrenal hyperplasia have an ARMCS pathogenic variant. ARMCS is a tumor suppressor gene. The patient in this vignette not only has bilateral macronodular adrenal hyperplasia, but she also has a history of meningioma. Several studies have identified an association between ARMCS pathogenic variants and bilateral macronodular adrenal hyperplasia and meningiomas. Pathogenic variants in p53 (Answer D) are associated with Li-Fraumeni syndrome. Patients with this syndrome can have adrenal cortical carcinomas (which this patient does not have), sarcomas, and glioblastoma multiforme

The BRAF gene (Answer B) is associated with papillary thyroid cancer, melanoma, glioblastoma multiforme, and colorectal cancers. The RET proto-oncogene (Answer E) is responsible for multiple endocrine neoplasia type 2A and 2B, which is associated with pheochromocytoma. The MAX gene (Answer C) is associated with pheochromocytoma

Educational Objective:

Recommend genetic testing for pathogenic variants in the ARMCS gene in patients with bilateral macronodular adrenal hyperplasia.

7.1. A 66-year-old ♂ presents with an incidental 3.7-cm right adrenal mass with a round shape and a density of 10 Hounsfield units. He has prediabetes and hypertension. Exam: he has no supraclavicular fat pads, striae, or muscle weakness.
Lab: (8 AM): Plasma metanephrines: normal. Aldosterone 5 ng/dL (4-21 ng/dL). Renin: 1 ng/mL/h (0.6-4.3). Urinary free cortisol: 15 µg/24 h (4-50). A dexamethasone-suppression test documents the following cortisol values: 2.4 µg/dL and 2.6 µg/dL. The patient asks about his prognosis Which of the following best characterizes this patient's chances of developing overt hypercortisolism in the next few years?

A. <1%.
B. 5%
C. 10%
D. 25%
E. 50%

7.2. ANSWER: A) <1%

This patient has mild autonomous cortisol secretion. The risk of developing overt hypercortisolism from an adrenal incidentaloma is less than 1% (Answer A). Several studies have reported the incidence of patients developing overt hypercortisolism to be 0.0-0.65%. However, studies evaluating patients with an initially nonfunctional adrenal mass who subsequently develop mild autonomous cortisol secretion have reported a range from 3.1-8.1%, with pooled proportions for the development of mild autonomous cortisol secretion of 5.4%. This patient already has mild autonomous cortisol secretion, and the question posed is what is the chance that he will develop overt hypercortisolism.

Educational Objective:

Define the risk of a patient developing overt hypercortisolism in the setting of mild autonomous cortisol secretion

8.1. A 43-year-old ♂ is referred for evaluation of resistant hypertension and hypokalemia. BP: while taking Amlodipine, Carvedilol, Lisinopril, Metformin, and KCL 148/96 in his primary care physician's office 4 weeks ago. His primary care physician ordered measurement of aldosterone and plasma renin activity and then started Spironolactone 25 mg/day. The patient started Spironolactone but did not have his blood drawn until 3 weeks later. At his appointment today, BP: 133/86, and he feels well with no adverse effects from his medications.

Lab: Na: 142 mEq/L (136-142). K: 3.4 mEq/L (3.5-5). Serum aldosterone 35 ng/dL (4-21). Plasma renin activity: < 0.6 ng/mL/h (0.6-4.3). Which is the best next step in this patient's evaluation?

A. Perform adrenal CT.
B. Perform adrenal MRI
C. Stop carvedilol and Lisinopril for 2 weeks and measure aldosterone and renin activity again
D. Stop Spironolactone for 6 weeks and measure aldosterone and renin activity again
E. Substitute Eplerenone for Spironolactone

8.2. ANSWER: A) Perform adrenal CT

This patient has resistant hypertension and hypokalemia, and the index of suspicion for primary aldosteronism is very high. Case detection with the aldosterone-to-renin ratio is indicated and was indeed ordered. Of all medications, mineralocorticoid receptor antagonists are the most likely to interfere with screening because these drugs have a tendency to raise renin. However, if renin remains suppressed, the screen is valid despite the presence of any medications. Endocrine Society guidelines (see figure) recommend eliminating confirmatory testing from the evaluation when renin is suppressed, hypokalemia is present, and the aldosterone concentration is >20 ng/dL (>554.8 pmol/L), as is the case in this patient. Thus, the next step is adrenal CT (Answer A). If the renin level had not been low, the screen would not have been interpretable and would have required repeated testing. Volume and the renin-aldosterone axis might take up to 6 weeks (but typically only 2 weeks) to re-equilibrate after Stopping spironolactone (Answer D) is not required in this case.

8.3. ANSWER: A) Perform adrenal CT

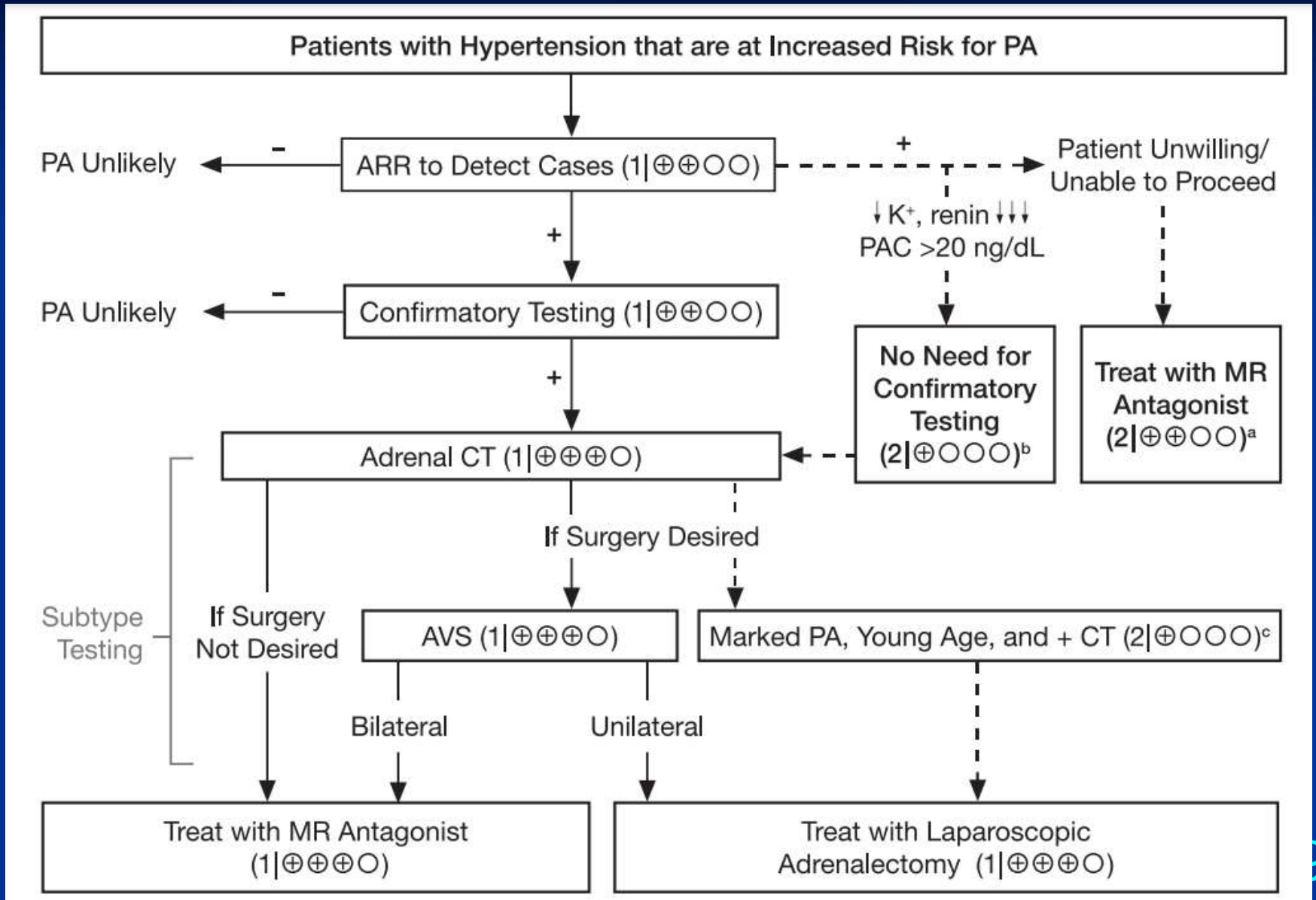
Similarly, discontinuation of other antihypertensive agents (Answer C) is not required for diagnosis if the renin is suppressed. MRI (Answer B) is inferior to CT due to low resolution.

The patient is tolerating spironolactone, so changing to eplerenone (Answer E), which is more expensive, is not necessary. In fact, all subsequent steps of the evaluation can be performed without stopping spironolactone, as long as the renin remains suppressed on that dosage. If the patient cannot or does not wish to pursue surgical management, medical therapy with a mineralocorticoid receptor antagonist should be continued. If the patient develops gynecomastia and/or erectile dysfunction from spironolactone, then substitution of eplerenone would be appropriate.

Educational Objective:

Guide screening and evaluation for primary aldosteronism

8.4. ANSWER: A) <1%:


Patients with Hypertension that are at Increased Risk for PA
PA Unlikely
-
ARR to Detect Cases (1|⊕⊕○○)
+
Patient Unwilling/ Unable to Proceed
↓K+, renin ↓↓↓ PAC >20 ng/dL
PA Unlikely
-
Confirmatory Testing (1|⊕⊕○○)
+
No Need for Confirmatory Testing (2|⊕○○○)b
Treat with MR Antagonist (2|⊕⊕○○)a
Adrenal CT (1|⊕⊕⊕○)
If Surgery Desired
Subtype Testing
If Surgery Not Desired
AVS (1|⊕⊕⊕○)
Marked PA, Young Age, and + CT (2|⊕○○○)c
Bilateral
Unilateral
Treat with MR Antagonist (1|⊕⊕⊕○)
Treat with Laparoscopic Adrenalectomy (1|⊕⊕⊕○)

8.5. ANSWER: A) <1%: Algorithm for the detection, confirmation, subtype testing, and treatment of PA. a We recommend unilateral laparoscopic adrenalectomy for patients with documented unilateral PA (ie, APA or UAH) (1 | QQQE). If a patient is unable or unwilling to undergo surgery, we recommend medical treatment including a MR antagonist (1 | QQQE). If an ARR-positive patient is unwilling or unable to undergo further investigations, we similarly recommend medical treatment including an MR antagonist (1 | QQEE). b Instead of proceeding directly to subtype classification, we recommend that patients with a positive ARR undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis (1 | QQEE). However, in the setting of spontaneous hypokalemia, undetectable renin, and PAC 20 ng/dL (550 pmol/L), we suggest that there may be no need for further confirmatory testing (2 | QEEE). c We recommend that when surgical treatment is feasible and desired by the patient, an experienced radiologist should use AVS to make the distinction between unilateral and bilateral adrenal disease (1 | QQQE). Younger patients (age 35) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions with radiological features consistent with a cortical adenoma on adrenal CT scan may not need AVS before proceeding to unilateral adrenalectomy (2 | QEEE).

9.1. A 51-year-old ♂ is present post-right open adrenalectomy for a 6-cm adrenocortical carcinoma that was causing Cushing's syndrome. The pathology specimen showed a high-grade tumor with vascular invasion, but no inferior vena cava thrombosis or lymph nodes were positive for the tumor. Postoperatively, he was treated with Hydrocortisone 20 mg upon waking and 10 mg in the afternoon, and he recovered well with some resolution of Cushingoid features. After 4 weeks, adjuvant Mitotane was added and titrated up to 6 g/day. Now, at a clinic visit 10 weeks later, his serum Mitotane value is at therapeutic goal, but he reports nausea, anorexia, and fatigue. BP: 125/82. without an orthostatic drop. Lab: Serum mitotane 16.4 mg/L (therapeutic goal >14 mg/L)
Serum K: 4.2 mEq/L (3.5-5). Plasma ACTH < 2 pg/mL (10-60). Serum total testosterone: 480 ng/dL (300-900). SHBG 11.5 µg/ml (1.1–6.7). Which is the best next step in this patient's management?

A. Add Fludrocortisone 0.1 mg/day
B. Add Testosterone enanthate 100 mg/week
C. Change hydrocortisone dosage to 25 mg in the morning 20 mg in the afternoon, and 5 mg in the evening.
D. Change hydrocortisone to Methylprednisolone 4 mg/day
E. Reduce mitotane dosage to 0.5 g 4 times/day

9.2. ANSWER: C) Change hydrocortisone dosage to 25 mg in the morning, 20 mg in the afternoon, and 5 mg in the evening

Mitotane therapy is typically prescribed for residual adrenal cancer following debulking surgery or as adjuvant therapy for high-risk disease. Mitotane has several adverse effects and alters endocrine laboratory tests through a variety of mechanisms, including direct adrenal cytotoxicity. This patient had Cushing syndrome before surgery, and debulking has left him with adrenal insufficiency due to a temporarily suppressed hypothalamic-pituitary-adrenal axis, as evidenced by undetectable plasma ACTH. At the same time, mitotane markedly increases corticosteroid-binding globulin and potently induces expression of CYP3A4, a major enzyme in cortisol catabolism. As a consequence, the dosage requirement and frequency of oral hydrocortisone increase with concomitant mitotane therapy, and this patient's symptoms of adrenal insufficiency are due to inadequate cortisol exposure (thus, Answer C is correct).

9.3. ANSWER: C) Switching to methylprednisolone (Answer D) would require higher equivalent doses. Although methylprednisolone does not depend on activation through 11β-hydroxysteroid dehydrogenase, it is, like all other glucocorticoids, still metabolized and inactivated by CYP3A4. Mitotane rarely causes aldosterone deficiency, and this patient is not volume depleted, so fludrocortisone at the dosage of 0.1 mg daily (Answer A) would not provide benefit. He is at high risk of cancer recurrence, and reducing the mitotane dosage (Answer E) would result in subtherapeutic drug levels, which is unwise. Hypogonadism and gynecomastia can occur with mitotane therapy due to an increase in SHBG and some inhibition of testosterone synthesis, but his testosterone and inferred bioavailable testosterone are normal and do not account for his symptoms. Thus, adding testosterone enanthate (Answer B) is incorrect.

Educational Objective:

Adjust the dosage of hydrocortisone during mitotane therapy for adrenal carcinoma

10.1. An 18-year-old college freshman is referred for evaluation of possible adrenal insufficiency. He has a two-year history of gradually increasing anorexia, fatigue, weakness, and weight loss. He is struggling to get to classes on time and to keep up with his studies. His family history is negative for adrenal disease, but a maternal uncle died suddenly after developing progressive weakness in his 20s. Exam: he is thin, has hyperpigmentation in sun-exposed areas but no vitiligo, and has orthostatic hypotension. He has diffuse muscle weakness, unsteady gait, and brisk deep tendon reflexes.
Initial lab: (from evaluation at the college student health center):
Plasma ACTH-144 pg/mL (10-60). Serum cortisol 3.7 µg/dL. Serum aldosterone <2 ng/dL (4-21). Plasma renin activity 24 ng/mL/h (0.6-4.3). Which diagnostic tests is most likely to reveal the etiology of his adrenal insufficiency?

A. Adrenal CT
B. Plasma lupus anticoagulant assessment
C. Plasma very long-chain fatty acid measurement.
D. Serum 21-hydroxylase antibody assessment
E. Urine synthetic glucocorticoid testing

10.2. ANSWER: C) Plasma very long-chain fatty acid measurement

The finding of primary adrenal insufficiency in a young man should always raise the suspicion of adrenoleukodystrophy (ALD), particularly when concurrent neurologic symptoms are present (see figure). ALD is an X-linked inherited metabolic storage disease associated with a defect in an ABC transporter that results in defective peroxisomal B-oxidation and accumulation of very long-chain fatty acids (C24, C26) in tissues, especially in the brain and the adrenal glands. The accumulation of very long-chain fatty acids causes demyelination associated with an intense inflammatory response in white matter. Neurologic manifestations include Psychiatric symptoms, neuromuscular problems, slurred speech, and even dementia are common symptoms. When mild, the condition is often misdiagnosed as multiple sclerosis or another primary neurologic disease. ALD affects approximately 1 in 17,000 boys, and female carriers can be symptomatic neurologically, but rarely, if ever, develop adrenal insufficiency.

10.3. ANSWER: C) Plasma very long-chain fatty acid measurement

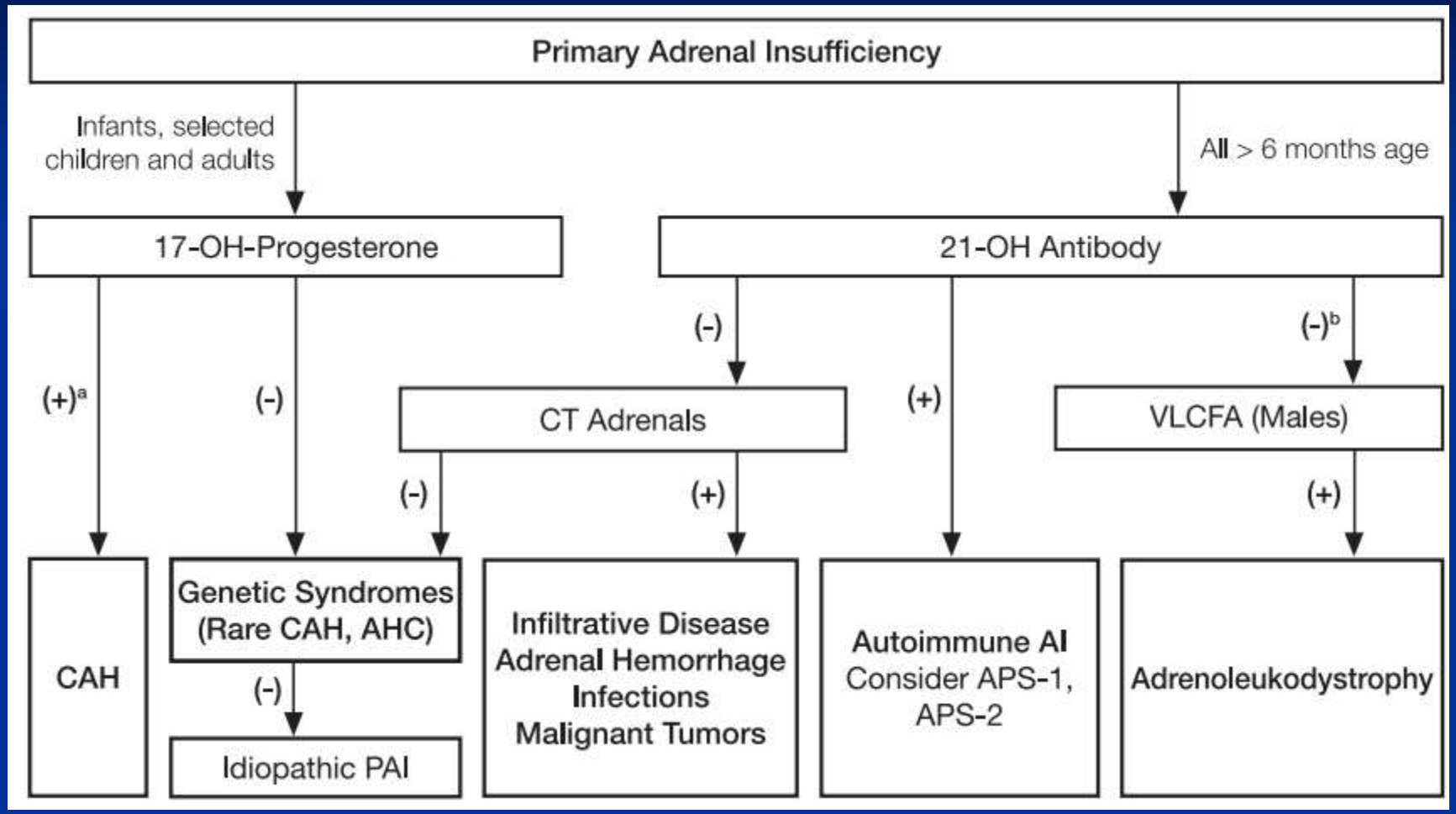
Approximately 70% of boys with ALD develop adrenal insufficiency. The finding of elevated plasma very long-chain fatty acids (Answer C) is highly reliable, and the diagnosis can be confirmed by genetic testing of the ABCDI gene. Adrenomyeloneuropathy is a milder form of this disorder that can coexist with ALD in the same family. Adrenomyeloneuropathy may present as primary adrenal insufficiency in young male patients, and the milder neurologic deficits carry a more favorable prognosis. Bone marrow transplantation is curative if diagnosed before the cerebral disease has progressed beyond recovery.

Serum 21-hydroxylase antibodies (Answer D) are used to diagnose autoimmune adrenal insufficiency. Lupus anticoagulant (Answer B) is often present with adrenal hemorrhage. Occult corticosteroid use (Answer E) would suppress—not raise—ACTH. Adrenal CT (Answer A) would show small adrenal glands in both ALD and autoimmune adrenalitis

Educational Objective:

Perform the differential diagnosis of adrenal insufficiency in a young man.

10.4. ANSWER: C) Plasma very long-chain fatty acid measurement



10.5. ANSWER: C) Plasma very long-chain fatty acid measurement

Algorithm for the diagnostic approach to the patient with PAI. The most common causes of PAI are autoimmune destruction of the adrenal cortex in adults and CAH in children. These etiologies can be screened for using 21-hydroxylase antibodies and a baseline serum 17-hydroxyprogesterone level. Males with negative 21-hydroxylase antibodies should be tested for adrenoleukodystrophy with plasma VLCFAs. If these diagnoses are excluded, a CT scan of the adrenals may reveal evidence of adrenal infiltrative processes or metastases. The individual's clinical picture and family history may render some steps in the algorithm redundant or suggest specific genetic syndromes. The latter includes subtypes of autoimmune polyglandular syndromes or specific rare genetic disorders where adrenal failure is part of a broader phenotype. A list of differential diagnoses is provided in Table 2. AHC, adrenal hypoplasia congenita; AI, adrenal insufficiency; VLCFA, very long chain fatty acid. a 17-OHprogesterone 1000 ng/dL is diagnostic for 21-OH deficiency (14). b VLCFA should be measured in the initial evaluation of preadolescent boys.

11.1. A 35-year-old ♀ with a history of Cushing's disease presents for annual follow-up. She developed depression and hypertension 5 years ago, and after diagnosis she underwent transsphenoidal surgery. Her condition improved postoperatively, and she took hydrocortisone for 12 weeks, at which time her adrenal function recovered.

Exam: today: she has no moon facies, plethora, dorsocervical fat pad, weakness, or bruises. Electrolytes are normal. She has developed borderline hypertension (145/88) and has gained 4 kg. Height: 168 cm, weight: 84 kg. BMI 29.8 kg/m².

Which diagnostic procedures should be recommended for further evaluation regarding recurrence in this patient?

A. Inferior petrosal sinus sampling with desmopressin hormone stimulation
B. Late-night salivary cortisol measurement.
C. 1-mg overnight dexamethasone-suppression test
D. 8-mg overnight dexamethasone-suppression test
E. 24-hour urinary free cortisol measurement

11.2. ANSWER: B) Late-night salivary cortisol measurement

The loss of cortisol diurnal rhythm is a defining feature of Cushing's disease. Saliva is an ultrafiltrate of plasma, and salivary cortisol concentrations roughly reflect plasma free cortisol concentrations. At night, plasma cortisol concentrations fall, and salivary cortisol decreases in parallel. Salivary cortisol testing has become routine and offers comparable diagnostic utility and greater convenience than late-night serum cortisol testing. In addition to its utility as a screening test for Cushing's disease, late-night salivary cortisol measurement (Answer B) is more sensitive than other conventional tests in detecting recurrent disease. False-positive results with late-night salivary cortisol measurement occur in persons with gingival or tongue bleeding, sleep disturbance, or who work night shifts. Also, contamination can influence test results, such as transfer of hydrocortisone cream from the hands to the device used to collect the saliva.

11.3. ANSWER: B) Late-night salivary cortisol measurement

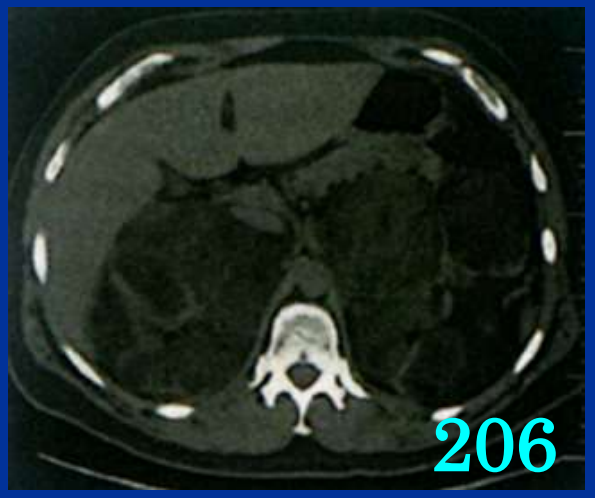
Measurement of 24-hour urinary free cortisol (Answer E) is relatively insensitive in detecting recurrent Cushing disease because only a small fraction (<1%) of cortisol is excreted unmetabolized and only when the cortisol concentration exceeds the binding capacity of plasma. Dexamethasone-suppression testing (Answers C and D) uses the empirically attenuated feedback inhibition of the pituitary adenoma to dexamethasone, compared with the normal pituitary. This distinction is not as reliable as the loss of diurnal rhythm in early, recurrent Cushing disease. Inferior petrosal sinus sampling (Answer A) is only used to exclude ectopic ACTH syndrome after the diagnosis of ACTH-dependent hypercortisolism is established.

Educational Objective:

Compare the diagnostic performance of different testing approaches for recurrent Cushing disease.,

12.1. A 29-year-old ♂ who was seen two years ago presents to the emergency department. The patient is intoxicated and has been experiencing abdominal pain and vomiting. He reports adrenal insufficiency and has a wallet card confirming this The emergency department physician asks for help reviewing the patient's abdominal CT (see image). Bilateral 16-cm heterogeneous adrenal masses are visible. Review of the clinic note from 2 years ago indicates that a firm lump in the right testis had been assessed at that time. After recommending IV Hydrocortisone, which of the following diagnoses should the emergency department physician be told that this man most likely has?

A. Autoimmune polyglandular syndrome type 2.
B. Bilateral adrenal hemorrhage
C. Bilateral metastases to the adrenal gland from testicular carcinoma
D. Congenital adrenal hyperplasia.
E. Histoplasmosis



12.2. ANSWER: D) Congenital adrenal

This patient's CT shows massive bilateral adrenal myelolipomas. These lesions are easy to identify on CT because they always have very low Hounsfield units (<10). Myelolipomas are benign neoplasms composed of mature adipose tissue, bone, and hematopoietic tissue. Myelolipomas have been reported in patients with congenital adrenal hyperplasia (CAH) (Answer D) due to a deficiency of 21-hydroxylase, 17-hydroxylase, or 11-hydroxylase. Most of these individuals have either untreated or poorly treated CAH. Patients with CAH sometimes have no ill effects over many months or years from cessation of steroid therapy until serious illness develops.

Chronic exposure of the adrenal glands to high ACTH concentrations is speculated to increase the risk of developing myelolipomas. In 1950, Selye and Stone transformed adrenal tissue in rats into adipose and bone marrow elements by injecting pituitary gland extract in combination with methyltestosterone. Myelolipomas have also been reported in patients with other disorders associated with chronic ACTH hypersecretion, including Cushing disease, Addison disease, and Nelson syndrome.

12.3. ANSWER: D) Congenital adrenal

Although some of the answer choices would explain adrenal insufficiency, there are no known reports of adrenal myelolipomas in patients with histoplasmosis (Answer E) or autoimmune adrenal disease (Answer A). Adrenal enlargement in patients with metastatic disease (Answer C) and bilateral adrenal hemorrhage (Answer B) has a heterogeneous appearance with an indeterminate attenuation value (>20 Hounsfield units). Decreased fertility is common in men with CAH and may be related to disordered adrenal metabolism and the development and growth of testicular adrenal rest tumors. Since these lesions are quite common in men with CAH, it is currently recommended that testicular ultrasonography be performed routinely in young men with this condition.

Educational Objective

Diagnose adrenal myelolipomas as a complication of poorly controlled congenital adrenal hyperplasia

13.1. A 61-year-old ♀ with a 50-pack-year history of cigarette smoking presents with recent-onset hypertension and peripheral edema. She appears to be cachectic and chronically ill. BP: 182/104, Pulse: 94. She has 4+ pretibial edema and severe muscle weakness.
Lab: Na 134 mEq/L (136-142). K: 2 mEq/L (3.5-5). Cl: 90 mEq/L (96-106). Bicarbonate: 42 mEq/L (21-28). Urea: 22 mg/dL (8-23). Cr: 0.7 mg/dL (0.6-1.1). Aldosterone <1 ng/dL (4-21). Plasma renin activity: < 0.1 ng/mL/h (0.6-4.3). Spironolactone, KCl, and Valsartan are initiated. CT of the chest and abdomen shows bilateral adrenal enlargement, with a 2-cm left adrenal nodule (10 Hounsfield units), and a large left inferior lobe lung mass. Which is the most likely cause of hypertension and hypokalemia in this patient?

A. Adrenocortical carcinoma with pulmonary metastases
B. Bilateral adrenal hyperplasia secreting aldosterone
C. Ectopic ACTH-secreting small cell lung cancer.
D. Fibromuscular dysplasia
E. Liddle syndrome

13.2. ANSWER: C) Ectopic ACTH-secreting small cell carcinoma of the lung.

The presence of hypertension with hypokalemic metabolic alkalosis and edema suggests a state of mineralocorticoid excess. However, this patient has suppressed plasma renin activity and aldosterone, which suggests excess of some other mineralocorticoid-like steroid. Of course, the most likely steroid is cortisol. Neither primary aldosteronism (Answer B) (elevated aldosterone, suppressed plasma renin activity) nor fibromuscular dysplasia (Answer D) (increased plasma renin activity and activation of the renin-angiotensin system) is possible. Fibromuscular dysplasia is a condition where there is abnormal growth in the walls of the artery, leading to narrowing that causes renovascular hypertension. The most likely cause of hypercortisolism in a patient with a long history of cigarette smoking and a lung mass is ectopic ACTH-secreting small cell lung cancer (Answer C).

13.3. ANSWER: C) The prevalence of lung cancer in women is increasing. The prodigious hypercortisolism seen in these patients overwhelms intrarenal cortisol metabolism and results in a state of mineralocorticoid excess with suppressed plasma renin activity and aldosterone. Because of the catabolic nature of severe hypercortisolism and metastatic disease, patients with ectopic ACTH syndrome often present as cachectic and malnourished, with muscle weakness due to steroid-induced myopathy as a leading symptom. Adrenocortical carcinoma (Answer A) occasionally presents with severe hypercortisolism and hypokalemia. However, adrenocortical carcinoma neoplasms are usually very large (>4 cm) and have an indeterminate attenuation value (Hounsfield units >20). In addition, one would not expect the contralateral adrenal gland to be enlarged due to the autonomous adrenal-dependent cortisol production from the adrenocortical carcinoma.

13.4. ANSWER: C) Liddle syndrome (Answer E) is an autosomal dominant form of hypertension due to pathogenic variants in the genes encoding subunits of the amiloride-sensitive epithelial sodium channel (SCNNIB or SCNNIG). This syndrome usually presents in childhood or early adulthood and is not associated with any adrenal enlargement The aldosterone-to-plasma renin activity ratio can provide useful clinical information in any patient with hypokalemia and hypertension. Elevated ratios (i.e., plasma aldosterone [PAC]/plasma renin activity [PRA] greater than or equal to 20 (555 in SL units)) suggest autonomic aldosterone secretion (primary aldosteronism). Elevations of both PAC and PRA (normal ratio) may be seen in all causes of renovascular hypertension, diuretic use, renin-secreting tumors (rare), malignant phase of hypertension, and coarctation of the aorta.

13.5. ANSWER: C) However, low levels of PAC and PRA (normal ratio) may be caused by Liddle syndrome, Cushing syndrome, congenital adrenal hyperplasia (e.g., 11β-hydroxylase deficiency), exogenous mineralocorticoid, syndrome of apparent mineralocorticoid excess (11β-hydroxysteroid dehydrogenase deficiency), or deoxycorticosterone-secreting adrenal tumors. Aldosterone, like cortisol, has a diurnal rhythm, so sampling should ideally be performed in the morning. Because the presence of marked hypokalemia may attenuate aldosterone secretion, potassium levels often need to be restored to normal (without a mineralocorticoid receptor antagonist) to accurately interpret the PAC.

Educational Objective:

Perform the differential diagnosis of hypertension, hypokalemia, and subnormal plasma renin and aldosterone

14.1. A 28-year-old ♂ was diagnosed with autoimmune adrenal insufficiency and hypothyroidism. He initially presented with a 11.4 kg weight loss and an adrenal crisis during a gastrointestinal illness. He was discharged from the hospital taking Hydrocortisone 20 mg upon waking in the morning and 10 mg in the early afternoon, as well as Levothyroxine 125 mcg/day. He regained most of his lost weight over the next 6 months and remained well without additional crises. For convenience, his glucocorticoid was changed to Methylprednisolone 6 mg upon waking. He has continued to slowly regain his lost weight, but he is now experiencing a generalized feeling of fatigue throughout the day, which does not improve shortly after taking the Methylprednisolone. He has even tried dividing his daily dose (3 mg upon waking and 3 mg in the early afternoon), but this has not relieved the fatigue following either dose On physical examination, his blood pressure is 104/66 mmHg and pulse rate is 88 beats/min. He has no purple striae, facial rounding, dermal atrophy, vitiligo, or bruises. Lab: Na: 138 mEq/L (136-142). K: 4.9 mEq/L (3.5-5).Plasma ACTH 400 pg/mL (10-60). Plasma renin activity: 13.4 ng/mL/h (0.6-4.3). TSH 2.2 mIU/L (0.5-5). Which changes is the best management recommendation?

A. Add Fludrocortisone acetate, 0.1 mg/day.
B. Administer methylprednisolone, 4 mg upon waking and 2 mg at bedtime
C. Reassure him that no changes are necessary
D. Switch Methylprednisolone to Dexamethasone, 1 mg upon waking
E. Switch Methylprednisolone to Hydrocortisone, 20 mg upon waking

14.2. ANSWER: A) Add fludrocortisone acetate, 0.1 mg daily

Adrenal replacement therapy is guided primarily by clinical parameters with limited laboratory testing. Specifically, plasma ACTH does not normalize with physiologic replacement doses and should not be used to titrate glucocorticoid in the same way that TSH is used to guide thyroxine replacement. Weight regain is a good sign that glucocorticoid dosing is adequate, and the absence of Cushingoid stigma suggests that he is not overtreated. Fatigue persists in some patients, and if it is due to glucocorticoid deficiency, this will transiently improve following each dose, which is not the case in this man Consequently, a more distributed dose of methylprednisolone (Answer B) is not going to help, and a bedtime dose of glucocorticoid is generally unnecessary for patients with adrenal insufficiency (except in the setting of congenital adrenal hyperplasia to lower cortisol precursor production). A single morning dose of hydrocortisone (Answer E) is sometimes sufficient for partial secondary adrenal insufficiency, but it is most likely not going to provide adequate exposure throughout the day in a patient with primary adrenal insufficiency.

14.3. ANSWER: A) Add fludrocortisone acetate, 0.1 mg daily

Chronic volume depletion is another cause of fatigue in patients with adrenal insufficiency. This patient has constant fatigue, a mild increase in heart rate, and borderline-low blood pressure.

More importantly, the plasma renin activity is quite elevated and the serum potassium value is high-normal. The patient was asked to stand for 2 minutes, and his blood pressure fell to 88/66 mmHg and pulse rate rose to 115 beats/min. Hydrocortisone (cortisol) is a mineralocorticoid, but the enzyme 11β-hydroxysteroid dehydrogenase type 2 inactivates most of the cortisol before it binds to the mineralocorticoid receptor. Hydrocortisone dosages of roughly 25 mg daily or more provide a variable amount of mineralocorticoid activity. In this patient, 30 mg daily was sufficient to maintain his volume status. In contrast, neither methylprednisolone nor dexamethasone (Answer D) provides much mineralocorticoid activity.

14.4. ANSWER: A) Add fludrocortisone acetate, 0.1 mg daily

With the switch from hydrocortisone to methylprednisolone, he has become volume He is depleted (thus, recommending no changes [Answer incorrect]), and he now needs fludrocortisone acetate therapy (Answer A). This scenario is often encountered in the setting of congenital adrenal hyperplasia, where the use of glucocorticoids ether than hydrocortisone is common. For many patients with primary adrenal insufficiency, the "standard" fludrocortisone dosage of 0.1 mg daily is adequate, and he might require a higher dosage to restore volume status and normalize plasma remineral activity and serum potassium.

Educational Objective:

Characterize the differences in mineralocorticoid activity of cortisol replacement therapies.

15.1. A 24-year-old ♂ is referred for evaluation of hypertension and low-normal K levels. He reports a family history of hypertension and states that his BP has been high since age 16. His current antihypertensive treatment regimen consists of Amlodipine, 5 mg daily, and Metoprolol, 25 mg daily. Both of his parents have hypertension; his father had a stroke at age 54. The patient's adrenal imaging shows a 1.2 cm nodule in the right adrenal gland and 0.6 cm and 0.8 cm nodules in the left adrenal gland.
Exam: BP: 172/98. Pulse: 72.
Lab: (9 AM): Na: 138 mEq/L (136-142). K: 3.5 mEq/L (3.5-5). Aldosterone 24.2 ng/dL (4-21 ng/dL). Plasma renin activity: 0.1 ng/mL/h (0.6-4.3). Plasma ACTH 38 pg/ml (10-60). Cortisol 12 µg/dL (5-25). Results of adrenal vein sampling are shown (done under cosyntropin stimulation in the early afternoon; peripheral vein baseline aldosterone concentration: 11 ng/dL and cortisol 8 µg/dL. Which of the following is the best next step in this patient's care?

Measurement	Right adrenal vein	Left adrenal vein	Inferior vena cava
Aldosterone	9220 ng/dL	22.520 ng/dl	118 ng/dL
Cortisol	539 mcg/dL	1247 mcg/dL	37 mcg/dL
Aldosterone/Cortisol	17	18	3

A. Measure metanephrines
B. Perform left adrenalectomy
C. Perform 1 mg dexamethasone-suppression test with next-morning aldosterone measurement.
D. Start spironolactone, 12.5 mg daily
E. Stop metoprolol and repeat screening

15.2. ANSWER: C) perform 1-mg 15 dexamethasone suppression test with next morning aldosterone measurement

This patient has primary aldosteronism with hypertension, low-normal potassium levels, and positive screening (renin suppressed and an aldosterone-to-renin ratio >20). The plasma aldosterone concentration is greater than 20 ng/dl (>554.8 pmol/L), and confirmatory testing is not necessary. He is young and has a longstanding history of hypertension and likely primary aldosteronism, suggesting a hereditary cause. Familial hyperaldosteronism (FH) has several subtypes:

FH type 1: glucocorticoid-remediable aldosteronism with a chimeric CYP1B1/CYP1182 gene

FH type 2: germline CLCN2 variants

FH type 3: germline KCNJS pathogenic variants

FH type 4: germline CACNAIH germline variants and primary aldosteronism with seizure syndromes (PASNA) syndrome; germline CACNAID variants

15.3. ANSWER: C) While most types of FH require genetic testing, FH type 1, glucocorticoid-remediable aldosteronism (GRA), can be detected by dexamethasone-suppression testing (Answer C). The genetic basis of GRA is a chimeric gene in which CYP11B2, an aldosterone synthase, harbors the CYPHBI promoter and becomes ACTH responsive. As in this case, there is an exaggerated response to cosyntropin stimulation, as seen with cosyntropin infusion during adrenal vein sampling. Suppressing the ACTH drive with dexamethasone suppression significantly reduces aldosterone levels, increasing suspicion for GRA, which can then be confirmed by genetic testing. Patients with GRA often have a family history of primary aldosteronism and stroke (usually hemorrhagic). GRA can be treated with low-dose dexamethasone suppression or spironolactone. However, the dosages needed are much >12.5 mg daily (Answer D). In a young man, eplerenone would be a better therapeutic option.

15.4. ANSWER: C) Bilateral adrenalectomy would cure GRA, but it would cause adrenal insufficiency, which confers greater morbidity than medical therapy. Left adrenalectomy (Answer B) would not cure the patient. Nodular adrenal glands are a common finding in GRA but are not the major source of aldosterone production. In general, only mineralocorticoid antagonists interfere with screening for primary aldosteronism. Metoprolol has a minor effect on renin levels, but it does not need to be stopped (Answer E) for screening.

The imaging characteristics of the adrenal nodules and the patient's history are not suggestive of a clinically significant pheochromocytoma. Therefore, measuring metanephrines (Answer A) is incorrect. Clinically significant pheochromocytomas are usually 3 cm or larger.

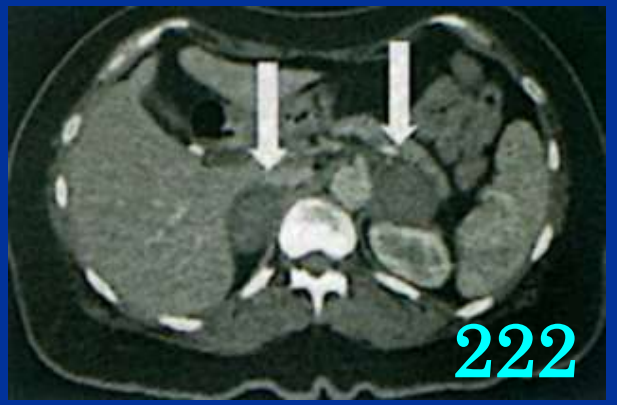
Educational Objective:

Construct the differential diagnosis of primary aldosteronism, including genetic causes.

16.1. A 69-year-old ♀ presents to the emergency department with abdominal pain, lethargy, fatigue, and nausea. Symptoms started 3 days ago and have been worsening. She had a hip replacement 10 days ago without complications. She has hypertension, which is controlled with Lisinopril 20 mg/day. She has no history of diabetes or osteoporosis. She does not smoke cigarettes. The abdomen is diffusely tender, and there is a healing scar on her right hip. Abdominal CT (with contrast) shows bilateral adrenal masses (60 Hounsfield units) (see image, arrows), and an endocrine consultation is sought.

Lab: Na: 128 mEq/L (136-142). K: 5.4 mEq/L (3.5-5). Serum cortisol (8 AM): 1.8 µg/dL (5-25). Serum DHEA-S 48 µg/dL (35-179). The patient is started on Hydrocortisone 50 mg every 8 hours. Which of the following is the best next step in this patient's management?

A. Adrenal mass biopsy
B. Chest/abdomen/pelvis CT
C. DOTATE-PET
D. FDG-PET
E. No further imaging or biochemical workup needed.



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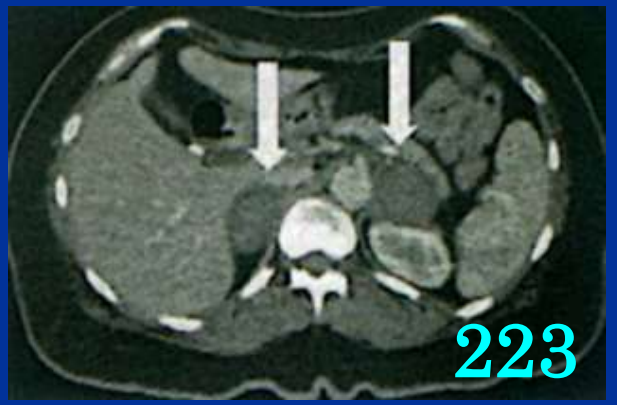


16.2. ANSWER: E) No further imaging or biochemical workup needed

This patient has symptoms and signs of acute-onset adrenal insufficiency, including nausea, abdominal pain, fatigue, and hypotension. In addition, she has bilateral adrenal masses, which appear well-rounded and circumscribed and are consistent with the diagnosis of bilateral adrenal hemorrhage. Therefore, no further imaging or testing is necessary now (Answer E). Patients undergoing hip replacement receive perisurgical anticoagulation, and this patient received warfarin, which resulted in bilateral adrenal hemorrhage and adrenal insufficiency. The correct therapy is immediate stress-dose hydrocortisone replacement The differential diagnoses for bilateral adrenal masses with adrenal insufficiency are congenital adrenal hyperplasia (hyperplasia or myelolipomas), infection (e.g., tuberculosis, histoplasmosis), adrenal lymphoma (often bilateral adrenal enlargement, somewhat respecting the adrenal shape), granulomatous disease, and bilateral adrenal hemorrhage.

16.3. ANSWER: E) No further imaging or biochemical workup needed

A relatively normal DHEA-S concentration is suggestive of very recent onset primary adrenal insufficiency (longer half-life than cortisol). Bilateral adrenal metastases are common in patients with cancer and can be the initial finding for a cancer diagnosis. Both pan-CT (Answer B) and FDG-PET (Answer D) would be reasonable choices to determine the full extent of the disease. However, adrenal metastases from solid tumors rarely cause adrenal insufficiency.

Adrenal mass biopsy (Answer A) is reserved for instances when determining the adrenal mass pathology makes a difference in care (e.g., a patient with lung cancer who has an adrenal nodule).

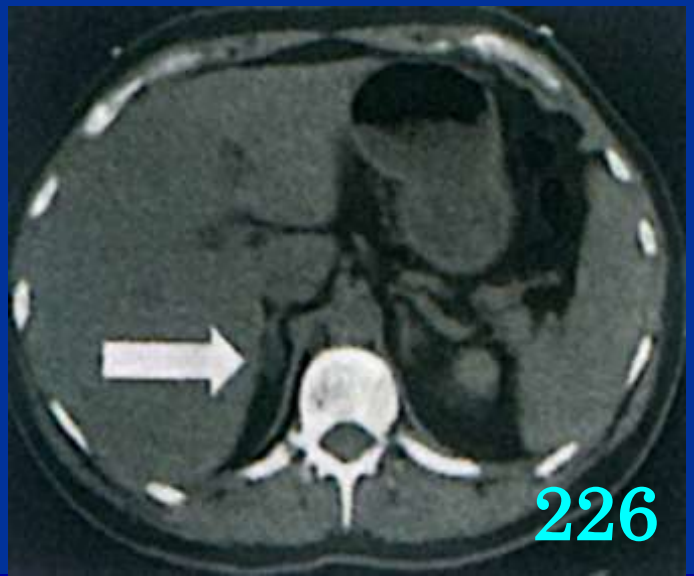
Regarding this patient's history, there is no concern for bilateral adrenal pheochromocytomas. Also, pheochromocytomas do not cause adrenal insufficiency. Thus, DOTATATE-PET (Answer C) is not necessary.

Educational Objective:

Diagnose and treat patients with adrenal insufficiency in the setting of bilateral adrenal masses

17.1. A 58-year-old ♀ is referred for an incidentally discovered 17-unit adrenal nodule. She had a recent emergency department visit for abdominal pain, which improved without therapy. She is otherwise healthy and does not have hypertension, osteoporosis, or diabetes. Her only medication is combined hormone replacement therapy, which she has been taking since age 49 A CT scan for suspected nephrolithiasis is performed, and it shows a 1.4-cm right adrenal mass with a density of 5 Hounsfield units (see image, arrow). Exam: she appears healthy. BP: 110/77, Pulse: 78. Height: 169 cm, weight: 60 kg. BMI: 21 kg/m². She has no hyperpigmentation, striae, or bruises.
Lab: Cortisol (following a 1-mg dexamethasone-suppression test) 1.2 µg/dL.
Na: 137 mEq/L (136-142). K: 4.2 mEq/L (3.5-5).
Which of the following describes the best follow-up care?

A. Measure aldosterone and renin
B. Measure plasma free metanephrine
C. Perform FDG-PET
D. Recommend no further evaluation now, follow-up with primary care physician.
E. Recommend no further evaluation now, follow-up with repeated CT in 1 year



17.2. ANSWER: D) Recommend no further evaluation now, follow-up with primary care physician

The workup of adrenal masses or nodules aims to answer two questions: (1) Is the mass benign or malignant? (2) Is there evidence of hormone excess? The first question can usually be answered by reviewing imaging. This mass is small, well-circumscribed, homogeneous, and has a density less than 10 Hounsfield units. Therefore, it is a benign adrenal nodule—a lipid-rich adenoma.

FDG-PET (Answer C), which is used for the differential diagnosis of benign and malignant nodules, is not necessary Biochemical evaluation for pheochromocytoma (Answer B) is indicated only if the mass has imaging criteria suggestive of pheochromocytoma or if there is clinical suspicion of a catecholamine-secreting tumor. This patient does not have classic spell-like symptoms, hypertension, or imaging consistent with a pheochromocytoma (Hounsfield units 10, often >20). She does not have symptoms or signs of overt adrenocortical hormone excess.

17.3. ANSWER: D) Screening for primary aldosteronism (Answer A) would only be necessary if she had hypertension or hypokalemia.
Despite the absence of overt hypercortisolism, screening for mild autonomous cortisol access (1-mg dexamethasone-suppression test) was performed, and the results were normal Initial workup of adrenal nodules should attempt to make a final diagnosis and define which patients would benefit from surgery. Only very few patients need to be followed (e.g., patients with indeterminate nodules who do not wish to undergo surgery, or those who have small, indeterminate nodules with mainly benign features). This patient has a nonfunctional, benign, lipid-rich adenoma. Such adenomas are present in 1% to 5% of the population and do not need dedicated follow-up (thus, Answer D is correct and Answer E is incorrect).

Educational Objective

Interpret findings from diagnostic procedures to evaluate incidentally discovered adrenal nodules

18.1. 18. A 64-year-old ♀ is referred for the incidental finding of a right adrenal nodule. On noncontrast CT, the homogeneous nodule measures 3.9 cm, with a density of 2 Hounsfield units. She has a history of borderline hypertension and postmenopausal osteoporosis, for which she is treated with Alendronate, 70 mg/week. She has gained 7 kg over the last 5 years. She has no concerns and feels well. After two years, she returns to the clinic. She is struggling with weight loss. She continues to take alendronate and has also started lisinopril for hypertension and Metformin. Exam: she has gained an additional 6 kg. Height: 162 cm, weight: 92 kg. BMI: 35. BP: 132/80, Pulse: 80. She has no facial plethora, dermal atrophy, bruising, or supraclavicular fat pads.

Which of the following is the best next step in this patient's care?

A. Delay medical or surgical therapy until urinary free cortisol is clearly elevated.
B. Measure cortisol after a high-dose (8 mg) dexamethasone-suppression test
C. Perform FDG-PET to evaluate for malignant transformation
D. Refer for laparoscopic right adrenalectomy.
E. Start osilodrostat, 2 mg twice daily

Lab results		
Analyte	2 years ago	Now
A1c	6.1%	6.9%
ACTH 8 AM	9 pg/mL	8 pg/mL
DHEAS	58 mcg/dL	< 15 mcg/dL
Cortisol after 1 mg dexamethasone	41 mcg/dL	41 mcg/dL
Urine free cortisol	22 mcg/24h	28 mcg/24h

18.2. ANSWER: D) Refer for laparoscopic right adrenalectomy

This patient has a diagnosis of mild autonomous cortisol excess (i.e., subclinical Cushing syndrome).

Despite the recommendation by some experts (American Association of Endocrine Surgeons) to surgically remove the adrenal tumor in all patients with mild autonomous cortisol excess, the general opinion is that patients for whom adrenalectomy might be beneficial should be very carefully selected. There is a growing body of literature that documents the long-term health consequences of mild autonomous cortisol excess derived from adrenal adenomas. These tumors are typically larger than 2.5 cm in diameter, as in this patient, and although exact minimum criteria for mild autonomous cortisol excess are debated, the three main tests (ACTH, DHEA-S, and dexamethasone-suppressed cortisol) are all consistently abnormal in this patient. She was initially clinically observed because she had osteoporosis and borderline hypertension, which are possible manifestations of hypercortisolism However, hypertension has now worsened, and she has developed obesity and diabetes.

18.3. ANSWER: D) Refer for laparoscopic right adrenalectomy

The DHEA-S concentration has further decreased due to persistent hypercortisolism of adrenal origin (suppression of pituitary ACTH drive). The major morbidity that improves with adrenalectomy is hypertension. However, autonomous cortisol excess from adrenal adenomas is associated with a host of other conditions, such as osteoporosis, glucose intolerance, cardiovascular events, and death, thus justifying the recommendation for surgical right adrenalectomy (Answer D). Retrospective and prospective studies have shown that patients without elevated urinary free cortisol excretion might benefit from surgery. Delaying medical or surgical therapy until urinary free cortisol is clearly elevated (Answer A) is incorrect. Also, this degree of cortisol excess can cause morbidities The patient does not have ACTH-dependent Cushing syndrome, and therefore a high-dose dexamethasone-suppression test (Answer B) is not indicated.

18.4. ANSWER: D) Refer for laparoscopic right adrenalectomy

There is also no concern for adrenocortical carcinoma, as there is only insidious worsening of symptoms, and the mass appears to be benign with a density less than 10 Hounsfield units. Therefore, imaging for malignant transformation (Answer C) is incorrect.

Surgery as a final therapy is preferred over any medical treatment, including mifepristone or osilodrostat (Answer E), which is indicated for patients with unsuccessful surgery or those who are not surgical candidates. Indeed, this patient needed postsurgical hydrocortisone replacement due to suppression of the contralateral adrenal gland—post-hoc evidence for presurgical hypercortisolism.

Educational Objective:

Identify patients with mild autonomic cortisol excess who might benefit from adrenalectomy

19.1. A 54-year-old ♂ with a history of fatigue and possible Cushing syndrome was referred for evaluation. His problems started after a back injury at work one year ago. He developed sudden lower back pain while lifting a heavy load and was sent home. He was evaluated and prescribed six weeks of physical therapy with some relief, followed by monthly back injections at a pain clinic for six months (these treatments ended four months ago). The injections markedly eased his pain, but he developed rapid weight gain, hunger, easy bruising, and facial fullness. Lab testing shows that his HbA1c A level has increased. Another lab: Urinary free cortisol: <3 µg/24 h (4-50).
Overnight 1-mg dexamethasone suppression test, cortisol < 0.2 µg/dL.
The patient is referred for further evaluation. He reports that his condition has not changed over the last 6 months. Exam: he has facial plethora and fullness, prominent supraclavicular fat pads, and dermal atrophy with diffuse bruising. BP: 125/80. His visual fields are full, and he has no pedal edema. Which diagnostic tests is most likely to reveal the etiology of his Cushing syndrome?

A. CT of the chest, abdomen, and pelvis
B. Late-night salivary cortisol measurement
C. ^{111}In-pentetreotide ("octreotide") scan
D. Pituitary MRI with contrast
E. Urine synthetic glucocorticoid testing.

19.2. ANSWER: E) Urine synthetic glucocorticoid testing

Corticosteroid injections for back pain are commonly administered in pain clinics, and patients are often unaware that the pain medicine is a mixture of anesthetics and potent synthetic corticosteroids. A typical history includes the abrupt onset of cushingoid features and metabolic consequences. Because these drugs do not activate the mineralocorticoid receptor as do high concentrations of cortisol, hypertension and hypokalemia are usually absent. When soluble preparations such as methylprednisolone are injected into the synovial fluid of a joint space, the drug is absorbed and cleared within several days, limiting the cumulative consequences. When a suspension preparation is injected into a relatively avascular space, the drug is absorbed very slowly, and the endocrinologic action can be profound and sustained. The most common agent causing long-term problems is triamcinolone acetonide, 0.1% suspensions, when given as facet joint or myofascial injections.

19.3. ANSWER: E) Urine synthetic glucocorticoid testing

The cumulative effect of 40 mg of triamcinolone acetonide is equivalent to roughly 1.2 g of hydrocortisone, more than the average person produces in 100 days. The particulate formulation prolongs the absorption of triamcinolone acetonide over weeks to months, creating a sustained toxic exposure. Patients with HIV infection taking the potent CYP3A4 inhibitor ritonavir are particularly susceptible due to the delayed metabolism of triamcinolone.

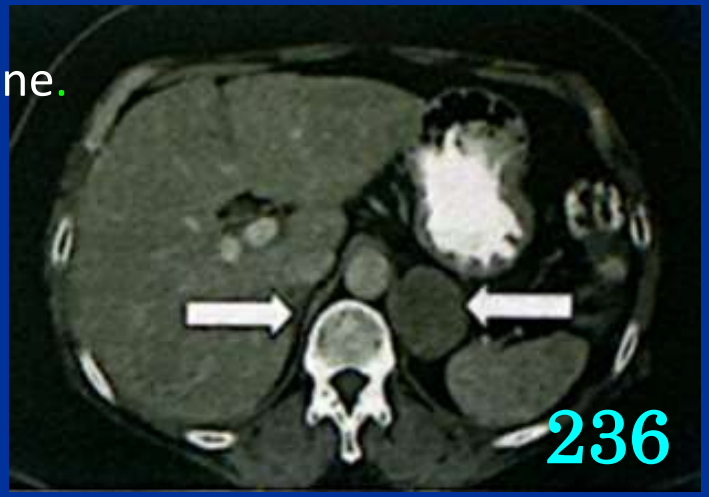
Although late-night salivary cortisol measurement (Answer B) might be the most sensitive test for ACTH-dependent hypercortisolism, this patient has low serum cortisol and plasma ACTH values, suggesting exogenous hypercortisolism. Imaging studies (Answers A, C, and D) would only be indicated if the screening laboratory tests suggested endogenous hypercortisolism. In this case, the urine synthetic glucocorticoid screen (Answer E) was positive for triamcinolone acetonide, despite the last injection being 4 months ago.

Educational Objective:

Confirm the diagnosis of iatrogenic Cushing syndrome and describe the magnitude and duration of glucocorticoid excess caused by injectable corticosteroids.

20.1. 20 A 45-year-old ♀ presents with resistant hypertension. She developed hypokalemia while taking Amlodipine and Hydrochlorothiazide. Lisinopril and KCl supplements, 80 mEq daily, were added with eventual resolution of the hypokalemia, but BP did not normalize. She has also gained 10 kg and developed prediabetes.
Exam: proximal muscle strength is normal. She has no plethora, dorsocervical fat pad, or striae. BMI: 34 kg/m^3, BP: 148/95. Lab: Na: 138 mEq/L (136-142). K: 3.6 mEq/L (3.5-5). Glucose 157 mg/dL (70-99). Serum aldosterone 13 ng/dL (4-21). Plasma renin activity < 0.6 ng/mL/h (0.6-4.3). Cr: 0.8 mg/dL (0.6-1.1 mg/dL). Plasma metanephrines, normal. Abdominal CT with contrast demonstrates a 3.8-cm left adrenal mass and an atrophic right adrenal gland (see image, arrows).
The patient is referred for further evaluation and recommendations.
Which of the following is the best next step in this patient's care?

A. Biopsy of the left adrenal gland
B. Measure serum cortisol after 1 mg of dexamethasone.
C. Prescribe spironolactone, 50 mg daily
D. Recommend left adrenalectomy
E. Schedule adrenal vein sampling to measure aldosterone and cortisol



20.2. ANSWER: B) Measure serum cortisol after 1 mg of dexamethasone.
Because of hypertension and hypokalemia, this patient was evaluated for primary aldosteronism, and the screening aldosterone-to-renin ratio was positive, but only modestly so. Normally, one would proceed to confirmatory testing, followed by CT, and then adrenal vein sampling to localize the source(s) of aldosterone. In this case, however, the weight gain, hyperglycemia, and dermal atrophy are suggestive of hypercortisolism as well Proximal myopathy and striae are late manifestations in the development of Cushing syndrome and are insensitive findings. Because a CT scan was performed, we know that she has a fairly large adrenal tumor—significantly larger than those that usually cause primary aldosteronism. Also, the contralateral (right) adrenal gland is somewhat atrophic, suggesting hypercortisolism from the left adrenal tumor. When the diameter of adrenal cortical tumors is > 2.4 cm, the risk of hypercortisolism increases, and if the tumor is removed without testing cortisol dynamics, an adrenal crisis might occur postoperatively.

20.3. ANSWER: B) Measure serum cortisol after 1 mg of dexamethasone.
In addition, diagnostic imaging in this vignette was only performed With contrast, one cannot use density to determine whether the tumor is lipid-rich, which would rule out pheochromocytoma. However, plasma metanephrines would be elevated if a mass this large were a pheochromocytoma. Spironolactone (Answer C) would treat the mineralocorticoid excess but not glucocorticoid manifestations, and this patient needs further evaluation before starting therapy.
Left adrenalectomy or biopsy (Answers A and D) is incorrect because possible hypercortisolism (and pheochromocytoma) must be ruled out before performing surgery or biopsy for a tumor of this size.
Adrenal vein sampling (Answer E) is the gold standard for lateralizing aldosterone production in primary aldosteronism, but if the tumor is cosecreting cortisol—which is used to correct adrenal vein aldosterone concentrations for dilution with mixed venous blood—the suppression of cortisol from the contralateral adrenal will artifactually raise the aldosterone-to-cortisol ratio on the contralateral side.

20.4. ANSWER: B) Measure serum cortisol after 1 mg of dexamethasone.

With the concern of hypercortisolism and the presence of a large adrenal tumor, performing a 1-mg overnight dexamethasone-suppression test (Answer B) is the best next step before deciding whether referral for surgery or venous sampling is necessary.

In this case, the overnight dexamethasone-suppression test resulted in a cortisol concentration of 4.4 µg/dL (121 nmol/L). Subsequent test results:

ACTH - 6.0 pg/mL (10-60 pg/mL) (SI: 1.3 pmol/L [2.2-13.2 pmol/L])

DHEA-S = 22 µg/dL (18-244 µg/dL)

Urinary free cortisol, normal

20.5. ANSWER: B) Thus, the diagnosis of ACTH-independent hypercortisolism was established, which overrides the evaluation of primary aldosteronism and indicates that the large left adrenal tumor should be removed with perioperative glucocorticoid coverage. Coproduction of aldosterone and cortisol from adrenal cortical adenomas, particularly larger tumors, is well described. It is possible, although unlikely, that primary aldosteronism is bilateral and unrelated to the adrenal tumor, so the patient This patient should be rescreened for primary aldosteronism after adrenalectomy. If it persists, spironolactone would be an appropriate treatment. After adrenalectomy, this patient had resolution of hypercortisolemia, hyperaldosteronism, and hypertension.

Educational Objective:

Suspect cortisol coproduction in patients with large aldosterone-producing adenomas.

21.1. A 28-year-old ♂ is referred for evaluation of possible adrenal insufficiency. He was seen in the emergency department 10 days ago for unexplained hypotension following a party, and an etiology was not identified. He recovered with fluid resuscitation and a single dose of Dexamethasone 10 mg IV. He received no further glucocorticoid treatment and takes no medication or nutritional supplements. Since discharge, he has had intermittent malaise and fatigue but no hypotension, and his appetite is normal. He comes to a clinic appointment today at 4 PM, and the question posed is whether adrenal insufficiency is the cause of his hypotensive episode. Which lab test result obtained at this time would conclusively rule out adrenal insufficiency?

A. Plasma ACTH concentration 10 pg/mL (6-48)
B. Salivary cortisol concentration: 0.1 µg/dL (0.01-0.2).
C. Serum cortisol concentration: 5 µg/dL (4-11).
D. Serum DHEA-S concentration: 360 µg/dL (38-523).

21.2. ANSWER: D) Serum DHEA-S concentration = 360 µg/dL (38-523)

The hypothalamic-pituitary-adrenal axis displays a prominent circadian rhythm, and these diurnal fluctuations in ACTH and cortisol production both guide and impede testing. A random serum cortisol measurement can be used to exclude adrenal insufficiency when it is above roughly 14 µg/dL (>386 nmol/L). ACTH is high in primary adrenal insufficiency and low in secondary adrenal insufficiency, and hence ACTH alone cannot diagnose adrenal insufficiency. Chances are best for obtaining a convincingly high value for cortisol in the early morning. Lower random values in the afternoon are typical, and while the laboratory might report a "normal range" for cortisol and ACTH in the afternoon, this normal range cannot be used to conclusively exclude adrenal insufficiency. Because cortisol has a short half-life of 30 to 60 minutes, dynamic testing is most commonly used It was used to rule out adrenal insufficiency in the afternoon.

21.3. ANSWER: D) Serum DHEA-S concentration = 360 µg/dL (38-523)

Alternatively, DHEA-S is also a measure of adrenal cortex function because it is produced in parallel with cortisol under ACTH stimulation. In contrast to cortisol, the half-life of DHEA-S is long (approximately 1 day), so little diurnal fluctuation is observed. Consequently, it is more likely that a conclusively normal DHEA-S value will be obtained in the afternoon (as opposed to cortisol), and a normal DHEA-S value in the absence of DHEA consumption rules out both primary and secondary adrenal insufficiency (thus, Answer D is correct). A single dose of dexamethasone will not suppress adrenal function for more than a few days, so random testing 10 days later is an appropriate screening method. The caveat with DHEA-S testing is that an age-related decline occurs, such that normal values are low when patients are older than about 64 years. An afternoon serum cortisol value of 5.0 µg/dL (138 nmol/L) (Answer C) might be in the "normal range" for that time of day, but the value would have to exceed roughly 14.0 µg/dL (>386 nmol/L) to exclude adrenal insufficiency. Random afternoon salivary cortisol testing (Answer B) has not been validated as a test of adrenal function, and ACTH values alone (Answer A) cannot be used to exclude adrenal insufficiency.

Educational Objective:

Use DHEA-S measurement in the evaluation of adrenal function.

22.1. A 34-year-old ♀ presents with rapidly progressive hirsutism, secondary amenorrhea, balding, voice deepening, and hypertension over the last 6 months. Her primary care physician has obtained some initial lab results: Na: 143 mEq/L (136-142). K: 3.1 mEq/L (3.5-5). Serum aldosterone < 4 ng/dL (4-21). Plasma renin activity: < 0.6 ng/mL/h (0.6-4.3). ACTH: 11 pg/mL (10-60). Serum cortisol (8 AM): 14 µg/dL (5-25). Serum DHEAS: 2833 µg/dL (44-352).
Serum 11-deoxycortisol 282 ng/dL (10-79). Serum total testosterone 310 ng/dL (8-60). SHBG: 1 µg/mL (2.2-14.6). Which of the following is the most likely diagnosis?

A. Adrenocortical carcinoma
B. Anabolic steroid abuse
C. Macronodular adrenocortical hyperplasia
D. Nonclassic 11-hydroxylase deficiency
E. Ovarian hyperthecosis

22.2. ANSWER: A) Adrenocortical carcinoma

Functional benign adrenal adenomas nearly always produce a single active hormone as their final product. Large cortisol-producing adenomas sometimes cosecrete aldosterone, but usually one hormone excess is dominant, while the second is mild. In contrast, overt, clinically manifested excess of more than one active steroid, such as glucocorticoid and androgen excess, is characteristic of adrenal cancer. Furthermore, the rapid progression of androgen excess alone, with very high testosterone and virilization (voice deepening), is worrisome for an adrenal or ovarian tumor. The mineralocorticoid excess in this patient, which is disproportionate to the cortisol and aldosterone concentrations, suggests an elevation of cortisol precursors, primarily corticosterone and 11-deoxycorticosterone Adrenal carcinomas (Answer A) tend to be relatively deficient in 11-hydroxylase activity, leading to elevated 11-deoxycortisol and further upstream intermediates.

22.3. ANSWER: A) This can account for the robust androgen and mineralocorticoid excess with normal or modestly elevated cortisol. In particular, the elevation of DHEA-S in parallel with testosterone and the 11-deoxycortisol elevation are almost pathognomonic for adrenal carcinoma. Hypokalemia in patients with adrenal cancer can arise from severe hypercortisolism overwhelming 11-hydroxysteroid dehydrogenase type 2 in the kidney, mineralocorticoid production, or compression of the kidney and renal vasculature.

Causing hyperreninemic hyperaldosteronism. Macronodular adrenocortical hyperplasia (Answer C) typically manifests with pure cortisol excess, and the mineralocorticoid excess is due to cortisol and parallel cortisol production. DHEA-S is usually normal in hypercortisolemic patients with macronodular hyperplasia rather than suppressed as is often the case in hypercortisolemic patients with unilateral adrenal cortical adenomas, but this preservation of DHEA-S does not account for the profound androgen excess in this patient.

22.2. ANSWER: A) While mild or nonclassic 11-hydroxylase deficiency (Answer D) has been described, these patients have mild androgen excess and rarely have Hypertension; the abrupt onset in this vignette is also inconsistent with a genetic etiology. Anabolic steroid abuse (Answer B) could account for the androgen excess but not the mineralocorticoid excess. Ovarian hyperthecosis (Answer E) is another cause of hirsutism and hyperandrogenemia. However, the onset is usually more insidious, and testosterone levels are not as elevated as they are in this patient. Most importantly, DHEA-S is usually not significantly elevated in the setting of ovarian hyperthecosis.

Educational Objective:

Suspect adrenocortical carcinoma on the basis of clinical features.

23.1. A 37-year-old ♀ with primary adrenal insufficiency presents for routine follow-up. She describes worsening anorexia and nausea. She has been on steady dosages of Hydrocortisone 15 mg in the morning upon awakening and 5 mg in the afternoon, and Fludrocortisone 0.1 mg/day. Adrenal insufficiency was initially diagnosed at age 24. She follows "sick day rules" and has injectable hydrocortisone at home. She has always been slightly hyperpigmented since diagnosis, but she has noticed worsening hyperpigmentation over the last 6 months. Over the last year, she started the following medications: combined oral contraceptives; biotin supplement (for subjective hair loss); Omeprazole 40 mg/day; and cholestyramine 8 g daily (for post cholecystectomy diarrhea). Diarrhea improved slightly, but it still persists. Over the last 6 weeks, she has lost 6 kg. Her current weight 58 kg. Exam: she appears less healthy than at previous visits. She is pale and has hyperpigmentation. Her blood pressure is 110/78 mmHg, and her pulse rate is 89 beats/min. Lab: Na: 130 mEq/L (136-142). K: 5.4 mEq/L (3.5-5). Plasma renin activity 60 ng/mL/h (0.6-4.3). Plasma ACTH 644 pg/mL (10-60). TSH 5.2 mIU/L (0.5-5). FT4: 1 ng/dL (0.8-1.8). Which is the most likely cause of this patient's concerns?

A. Atrophic gastritis
B. Cholestyramine
C. Combined oral contraceptive
D. Hashimoto's disease
E. Proton-pump inhibitor

23.2. ANSWER: B) Cholestyramine

This patient has longstanding adrenal insufficiency without a dosage change in hydrocortisone. She has symptoms and signs of adrenal insufficiency despite taking the same hydrocortisone dosage. When considering causes of insidious worsening of symptoms and signs of adrenal insufficiency, one should consider additional endocrinopathies, medication changes, or other systemic diseases. Autoimmune adrenalitis It occurs as part of other autoimmune disorders and endocrinopathies.

Cholestyramine (Answer B) is commonly used to treat chronic diarrhea due to its bile acid-sequestering properties. Cholestyramine also binds hydrocortisone and prevents its absorption. The patient should be advised to take hydrocortisone at least 1 hour before the cholestyramine, which usually resolves the issue.

While Hashimoto's disease (Answer D)

23.3. ANSWER: B) Cholestyramine

This might explain some of her symptoms. She does not have typical hypothyroid symptoms; her free T concentration is normal, and her TSH concentration is only slightly elevated. Hydrocortisone requirements are not typically affected by low thyroid hormone levels. An increased requirement would rather be expected with hyperthyroidism (e.g., Graves' disease), which leads to increased metabolism of hydrocortisone. Several medications can increase hydrocortisone requirements. Usually, inducers of CYP3A4 increase cortisol metabolism. While physiologically only a small fraction of cortisol is metabolized through 6α-hydroxylation by CYP3A4, induction of this enzyme can significantly increase this fraction.
Common inducers of CYP3A4 are mitotane, carbamazepine, phenytoin, and St. John's wort.

23.4. ANSWER: B) Cholestyramine

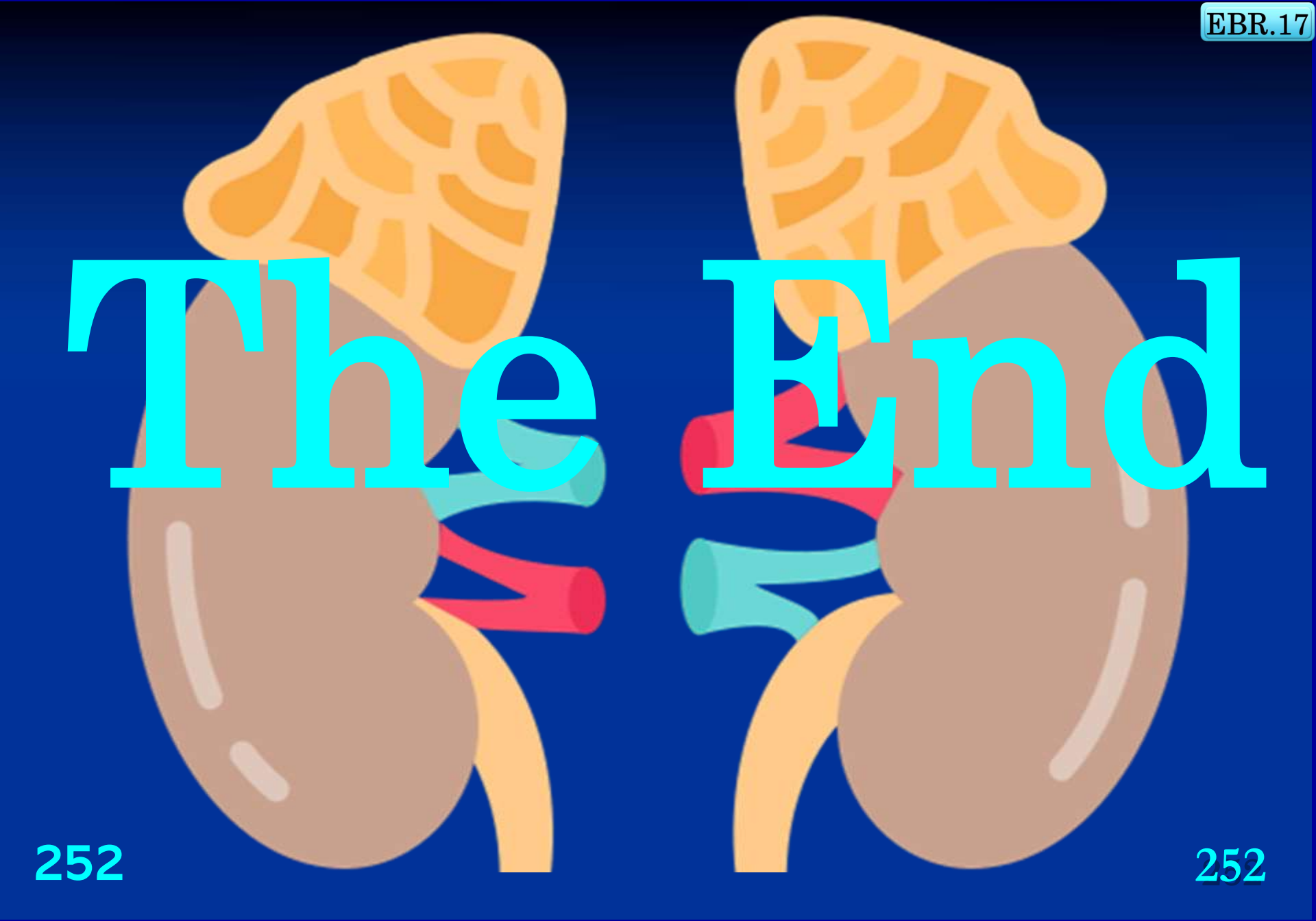
Proton-pump inhibitors (Answer E) are not known to influence hydrocortisone metabolism or absorption.

Estrogen-containing oral contraceptives (Answer C) increase cortisol-binding globulin and can pose a challenge when measuring total serum cortisol (e.g., 1-mg dexamethasone-suppression test), but there is no effect on the total daily hydrocortisone requirement.

Atrophic gastritis (Answer A) is commonly observed in patients with polyglandular autoimmune syndrome, but it does not alter hydrocortisone requirements. While biotin can interfere with several immunoassays, there is no biological effect that would require adjustment of the hydrocortisone dosage.

Educational Objective:

Identify medications that can alter hydrocortisone metabolism and absorption



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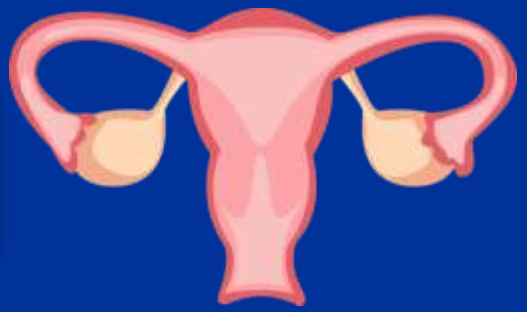
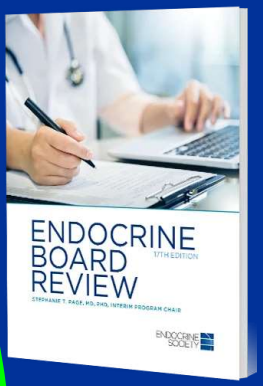
مراجعات البورد في الغدد

EBR.17

Female Reproduction

Female Reproduction





الدكتور محمد الشعباني

1.1. A 38-year-old ♀ presents for evaluation 1 of a hormonal disorder. She reports increased irritability and depressive thoughts leading up to her menses. She also describes bloating, breast tenderness, and fatigue. On day 2 of her menses, she feels back to normal. She cannot tolerate combined oral contraceptive pills because she feels they exacerbate her symptoms. She typically calls in sick at least one day a month because of these symptoms. She avoids social outings for the week before her menses. During her last cycle, she experienced an episode of suicidal ideation that required an emergency session with her psychologist. In addition to a copper intrauterine device, medications and supplements are fluoxetine, 60 mg daily; calcium, 1000 mg/day; and ibuprofen 400 mg every 6 hours as needed for pain. Which is the best next step to address this patient's symptoms?

A. Change fluoxetine administration to cyclically
B. Prescribe a GnRH agonist with sex steroid add-back (estradiol)
C. Recommend bilateral oophorectomy with hormone replacement therapy
D. Recommend cognitive behavioral therapy
E. Recommend complete hysterectomy with hormone replacement therapy

1.2. ANSWER: B) Prescribe a GnRH agonist with sex steroid add-back (estradiol)

The patient has severe premenstrual dysphoric disorder (PMDD). PMDD is distinguished from premenstrual syndrome by predominantly affective syndromes and the degree of impairment to family life, social life, and ability to work. She is on first-line therapy (selective serotonin reuptake inhibitor [SSRI]) at a maximum dosage. SSRIs may be administered cyclically (Answer A) or continuously; there is no need to change the frequency of administration. She is intolerant to combined oral contraceptive pills, which is more common when affective symptoms predominate. She is already seeing a psychologist, so there is no need to recommend additional cognitive behavioral therapy (Answer D). The next step is to consider a permanent solution. However, it is recommended to conduct a 2- to 3-month trial of GnRH agonist therapy with estradiol add-back (Answer B) before recommending surgery. Bilateral oophorectomy without hysterectomy (Answer C) would require estradiol and progesterone add-back; therefore, complete abdominal hysterectomy (Answer E), which requires only estradiol add-back, may have additional benefits. She is taking adjuvant supplements for which there is minimal evidence of benefit but limited risk for harm (calcium and ibuprofen).

Educational Objective:

Implement therapy for treatment-resistant premenstrual dysphoric disorder.

2.1. A 30-year-old ♀ presents with 2 primary infertility episodes. On initial workup, a microprolactinoma was diagnosed, and she was prescribed cabergoline, 0.5 mg twice weekly. For the past year, she has been having regular sexual intercourse. Her menstrual cycles remain irregular. Her male partner has normal findings on semen analysis.
Exam: BP: 118/78. BMI: 22. no hirsutism or acne.
Lab: (day 3 of cycle): FSH 4 mIU/mL (2-12). LH 2.5 mIU/mL (1-18). Estradiol 20 pg/mL (10-180). Prolactin 5 ng/mL (4-30). Testosterone: 15 ng/dL (8-60).
Which is the best next step in treating this patient's infertility?

A. Increase cabergoline dosage to 1 mg twice weekly
B. Refer for in vitro fertilization
C. Start gonadotropin therapy with menotropins
D. Start letrozole
E. Switch from cabergoline to bromocriptine

2.2. ANSWER: C) Start gonadotropin therapy with menotropins

Women with treated hyperprolactinemia may continue to experience compromised fertility. The appropriate fertility treatment is gonadotropin therapy (Answer C), and in vitro fertilization (Answer B) may also be needed. Given the mechanism of infertility (ongoing, lower-than-expected estradiol levels), letrozole (Answer D) is not indicated. While bromocriptine has more extensive safety data in early pregnancy than cabergoline, changing dopamine agonist therapy (Answer E) is not recommended. For patients with idiopathic hyperprolactinemia or a microprolactinoma, bromocriptine or cabergoline should be discontinued with the first positive pregnancy test. While increasing cabergoline may be considered in patients with persistently elevated prolactin levels, this patient has well-treated hyperprolactinemia

Educational Objective: Recommend the best treatment for hyperprolactinemia-mediated infertility.

3.1. A 21-year-old person with a history of self-care. She uses she/her pronouns and has presented as female for several years. She shaves or waxes to remove body and facial hair. She reports she does not like to look at her "male organ" and often "tucks it away." She is interested in gonadectomy and genital reconstruction surgery.
Exam: she has Tanner stage 5 male sexual development. Her mood and affect are appropriate Screening for depression reveals no significant active depressive symptoms. Her only medication is escitalopram, 10 mg daily. Which is the best next step in this patient's care?

A. Refer for psychiatric evaluation
B. Refer for surgical evaluation for gonadectomy and genital reconstruction surgery
C. Screen for contraindications to gender-affirming hormone therapy
D. Start GnRH agonist and estradiol, 0.5 mg daily
E. Start spironolactone, 100 mg twice daily

3.2. ANSWER: C) Screen for contraindications to gender-affirming hormone therapy: This patient is a trans woman and has demonstrated marked and sustained gender incongruence. In ICD-11, "Gender incongruence of adolescence and adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire for 'transition' in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery, or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.“ A single, appropriately trained healthcare provider is capable of determining whether a person is an appropriate candidate for gender-affirming care.

3.3. ANSWER: C) The criteria for gender-affirming care include marked and sustained gender incongruence, no other explanation for the gender incongruence, no significant untreated mental health disorder that could influence the patient's gender incongruence, and the patient's ability to consent to treatment. This patient does not require additional psychiatric evaluation for well-controlled depression (Answer A). Before initiating gender-affirming care (Answers D and E), the patient should be screened for contraindications to gender-affirming hormone therapy (Answer C). Screening includes documenting weight and blood pressure; performing a physical examination; and assessing tobacco use history, depressive symptoms, and family and personal history of clotting disorders and hormone-sensitive cancers. While the patient is specifically requesting nonhormonal surgery for gender-affirming care, it is recommended that she be treated for at least 6 months with gender-affirming hormone therapy before surgical intervention (Answer B).

Educational Objective: Recommend appropriate clinical care and screening for individuals with gender incongruence.

4.1. A 42-year-old transwoman presents for her annual physical exam. She reports that she has been in her usual state of health and has no concerns. Medications are leuprolide, 3.75 mg intramuscularly monthly, and estradiol, 2 mg orally daily.
Lab: (fasting): LDL: 116 mg/dL (<100). HDL: 70 mg/dL (>60). Tg: 450 mg/dL (<150). HbA1c: 5.5% (4-5.6%). Which is the best treatment option for this patient?

A. Change from estradiol, 2 mg orally/day, to estradiol, 0.1 mg/day transdermal
B. Change from leuprolide to spironolactone
C. Start atorvastatin 40 mg/day
D. Start fenofibrate, 160 mg/day
E. Stop leuprolide and estradiol

4.2. ANSWER: A) Change from estradiol, 2 mg orally daily, to estradiol, 0.1 mg daily transdermal: Gender-affirming hormone therapy with oral estradiol can raise triglycerides. If the patient demonstrates clinically significant increases in triglycerides, changing to transdermal estradiol (Answer A) would reduce triglycerides. There is no indication to stop the patient's gender-affirming care (Answer E). While leuprolide can modestly increase triglycerides, the most likely driver of this elevation (and the high HDL cholesterol) is oral estradiol. Thus, there is no need to switch leuprolide to spironolactone (Answer B).

The first option for treating the elevated triglycerides is to adjust medications that may be responsible, not start lipid-lowering therapy (Answers C and D).

Educational Objective:

Manage complications of gender-affirming hormone therapy.

5.1. A 51-year-old postmenopausal ♀ with a history of breast cancer presents for management of hot flashes. She reports daily hot flashes and vaginal dryness with pain during sexual intercourse. She experiences night sweats. Last menstrual period was 2 years ago. Last year, she completed a 5-year course of Tamoxifen, an adjuvant therapy for breast cancer. Lab: last annual physical appointment demonstrated normal cholesterol, metabolic panels, and liver function. Medications are Gabapentin 600 mg (7 AM and 3 PM) and 900 mg (at 11 PM) for neuropathic pain, and Citalopram 20 mg/day, for depression.
Which is the best treatment option for this patient?

A. Clonidine patch, 0.1 mg daily
B. Fezolinetant, 45 mg daily
C. Suvorexant 10 mg nightly
D. Transdermal estradiol, 25 mcg daily
E. Vaginal estradiol, 10 mg twice weekly

5.2. ANSWER: B) Fezolinetant, 45 mg daily: This patient remains significantly. Symptomatic on a selective serotonin reuptake inhibitor and gabapentin. However, she is not a candidate for menopausal hormone therapy (Answer D) due to her history of breast cancer. Fezolinetant (Answer B) is a neurokinin B receptor antagonist that is FDA-approved for the treatment of menopausal vasomotor symptoms. The most common adverse effect is headache. It is recommended that patients taking Fezolinetant have their liver enzymes monitored at baseline and at 1, 2, 3, 6, 9, and 12 months. In an evidence-based literature review by the North American Menopause Society, clonidine (Answer A) is not recommended because of limited efficacy and significant adverse effects. Suvorexant (Answer C) is not recommended due to a lack of improvement in daytime vasomotor symptoms. While vaginal estradiol (Answer E) may treat the patient's vaginal dryness, it would not address her chief concern—bothersome vasomotor symptoms.

Educational Objective: Recommend options for nonhormonal treatment of vasomotor symptoms of menopause.

6.1. A 17-year-old ♀ presents with primary amenorrhea. She reports normal breast development at age 10. She is otherwise healthy, and there is no family history of reproductive disorders. She is on the track team in high school and runs 15 miles weekly. Exam: BMI: 25. Height: 175 cm. BP: 120/80. She has Tanner stage 5 breast development and Tanner stage 2 axillary and pubic hair. A manual pelvic examination reveals no cervix.

Lab: FSH: 3.5 mIU/mL. LH: 18.5 mIU/mL. Estradiol: 30 pg/mL. SHBG: 6 µg/mL.

Which is the most likely diagnosis of this patient's pubertal disorder?

A. Androgen insensitivity syndrome
B. Autoimmune oophoritis
C. 5α-Reductase deficiency
D. Mayer-Rokitansky-Kuster-Hauser syndrome
E. Turner syndrome

6.2. ANSWER: A) Androgen insensitivity syndrome: This patient is phenotypically female with complete breast development and partial development of axillary and pubic hair. The absence of the cervix suggests Müllerian agenesis, with loss of the upper one-third of the vagina, cervix, uterus, and fallopian tubes. The differential diagnosis for these findings includes androgen insensitivity syndrome (Answer A) and Mayer-Rokitansky-Kuster-Hauser syndrome (Answer D). However, Mayer-Rokitansky-Kuster-Hauser syndrome is not associated with premature ovarian insufficiency or elevated LH levels. Androgen insensitivity syndrome is characterized by pathogenic variants in the gene encoding the androgen receptor in an individual with a 46,XY karyotype. In this case, the patient has complete androgen insensitivity syndrome. Therefore, she is phenotypically female with elevated LH levels and normal male testosterone levels.

6.3. ANSWER: A) Androgen insensitivity syndrome:

In androgen insensitivity syndrome, pubic and axillary hair is sparse due to a lack of androgen in combination with estrogen action. The testes are often located in the groin or abdomen and carry the potential for tumor formation (2%-5%). Gonadectomy after puberty should be a shared decision between the patient, family, and physician. If gonadectomy occurs, physiologic hormone therapy is recommended. Individuals with partial defects in the androgen receptor can present with genital atypia or even as phenotypic males with hypospadias, oligospermia, undervirilization, and infertility. Turner syndrome (Answer E) presents with premature ovarian insufficiency characterized by Low estradiol and elevated FSH, which this patient does not have.

6.4. ANSWER: A) Androgen insensitivity syndrome:

While autoimmune oophoritis (Answer B) can be a cause of premature ovarian insufficiency with a relatively preserved FSH level, this patient's FSH concentration is lower than expected.

5a-Reductase deficiency (Answer C) is an autosomal recessive disorder in which males with a 46,XY karyotype present with atypical genitalia and virilize to a more male phenotype at puberty.

Educational Objective:

Outline the manifestations and diagnosis of patients with androgen insensitivity syndrome.

7.1. A 20-year-old college student presents with a 4-month history of amenorrhea. She has fatigue and mild acne but no hirsutism. She has no headaches or vision symptoms. Her menstrual period started at age 14. She played sports in high school and occasionally missed a period. During college, her periods have been every 30-35 days. She attributes this to stress related to schoolwork. Her physical Exam: normal. Lab: FSH 1 mIU/mL (2-12). LH 2 mIU/mL (1-18). Estradiol 520 pg/mL (10-180). Prolactin 68 ng/mL (4-30). Which is the most likely diagnosis in this patient?

A. Hypothalamic amenorrhea
B. Polycystic ovary syndrome
C. Pregnancy
D. Primary ovarian insufficiency
E. Prolactinoma

7.2. ANSWER: C) Pregnancy. It is always critical to rule out pregnancy (Answer C) in a woman of childbearing age who presents with irregular menses or amenorrhea. Pregnancy can be detected by an elevated serum hCG value before the time of a missed menses or in a urine pregnancy test soon afterward. During early pregnancy, the estrogen level rises and suppresses gonadotropins. The extremely high estradiol and high prolactin rule out polycystic ovary syndrome (Answer B), which is a diagnosis of exclusion. A patient with a prolactinoma (Answer E) would present with low FSH, low LH, and low or low-normal estradiol because prolactin suppresses hypothalamic GnRH secretion. High FSH, high LH, and low estradiol would be seen in a patient with primary ovarian insufficiency (Answer D).
Low LH, low-normal FSH, and low estradiol would be seen in a patient with hypothalamic amenorrhea (Answer A).
Educational Objective: Identify the laboratory changes that would be anticipated in an amenorrheic patient who is pregnant.

8.1. A 22-year-old ♀ presents with hirsutism and irregular menses. She had early development of pubic hair at age 7. Menarche was at age 11. Her cycles have always been irregular

Exam: BMI 25. She has hair on her chin, upper lip, and neck, 8 hairs on her areolae, and hair to her umbilicus. She has no clitoromegaly.

Lab: (random cycle day): LH 5 mIU/mL. FSH: 4 mIU/mL. Estradiol 40 pg/mL. Testosterone: 50 ng/dL. DHEAS: 280 µg/dL.

17-OHP: 215 ng/dL (<285 [luteal phase]; <80 ng/dL (follicular phase)). <2.42 nmol/L (follicular). Prolactin 18 ng/mL (4-30). Which diagnoses best explains this patient's clinical presentation?

A. Adrenal Cushing syndrome
B. Nonclassic congenital adrenal hyperplasia
C. Polycystic ovary syndrome
D. Sertoli-Leydig-cell tumor of the ovary
E. Virilizing adrenal tumor

8.2. ANSWER: B) Nonclassic congenital 8-adrenal hyperplasia

Nonclassic congenital adrenal hyperplasia (CAH) (21a-hydroxylase deficiency) (Answer B) is a rare cause of hirsutism with irregular menses. The incidence varies from 1-10/20,000 live births. Nonclassic CAH is more common in those of Italian, Hispanic, Ashkenazi Jewish, and Eskimo descent. In women with nonclassic CAH, basal morning serum 17-OHP concentrations (during the follicular phase of the menstrual cycle) are usually greater than 200 ng/dL (>6.1 nmol/L) (high-normal or high). This patient has a normal LH value and an estradiol value consistent with the early follicular phase; therefore, 17-OHP is elevated, and the most likely diagnosis is nonclassic CAH. The diagnosis of nonclassic CAH is confirmed by documenting stimulated levels of 17-OHP >1000-1500 ng/dL (30.3-45.5 nmol/L) 30-60 minutes after cosyntropin stimulation.

8.3. ANSWER: B) Nonclassic congenital 8-adrenal hyperplasia

The cosyntropin-stimulation test should also assess peak cortisol levels to determine whether the patient needs glucocorticoid support before major surgery or during illness. Treatment of nonclassic CAH consists of a combination oral contraceptive with a less androgenic progestin and an androgen-receptor blocker (spironolactone) to treat the hirsutism until pregnancy is desired. Glucocorticoids are sometimes needed for ovulation induction to suppress circulating progesterone to allow optimal folliculogenesis and LH surge.

A patient with polycystic ovary syndrome (Answer C) could present with a scenario similar to that of this patient, but not with an elevated 17-OHP value. A virilizing adrenal tumor (Answer E) would present with a very high DHEA-S level (>800 µg/dL [>21.7 µmol/L]) or rarely a very high testosterone level.

8.4. ANSWER: B) Nonclassic congenital 8-adrenal hyperplasia

A patient with adrenal Cushing syndrome (Answer A) would present with low DHEA-S levels. One would perform a dexamethasone-suppression test to confirm the diagnosis. Ovarian tumors (Answer D) may make a combination of ovarian androgens, but affected patients usually have a testosterone level in the male range and would not just have an elevated 17-hydroxyprogesterone level.

Educational Objective:

Diagnose nonclassic congenital adrenal hyperplasia and evaluate a patient with hirsutism and irregular menses.

9.1. A 38-year-old ♀ with a history of PCOS presents for management of hirsutism. She also desires contraception. She has periods approximately every 3 months, sometimes with heavy bleeding. An endometrial biopsy performed by her gynecologist because of her infrequent menses and heavy bleeding showed proliferative endometrium. She was given a 10-day course of medroxyprogesterone acetate, 10 mg daily. She has longstanding hirsutism and has developed some female-pattern hair loss over the past 2 years. She has no history of clotting disorders, hypertension, diabetes, migraines, or dyslipidemia.

Exam: Ferriman-Gallwey score: 14. BMI 23, and she has Sinclair grade 2 female-pattern hair loss.

Lab: (day 3 cycle): Testosterone: 62 ng/dL (8-60). FSH: 9 mIU/mL (2-12).

Which is the best therapy to manage her symptoms and provide contraception?

A. Levonorgestrel-releasing intrauterine device and laser hair removal
B. Oral estrogen-progestin contraceptive (ethinyl estradiol, 20 mcg/norethindrone acetate, 1 mg)
C. Oral estrogen-progestin contraceptive (ethinyl estradiol, 50 mcg/norgestrel, 0.5 mg)
D. Progestin-only contraceptive (drospirenone 4 mg daily)
E. Spironolactone, 100 mg twice daily, and barrier contraception

9.2. ANSWER: B) Oral estrogen-progestin contraceptive (ethinyl estradiol, 20 mcg/norethindrone acetate, 1 mg)

This patient has oligomenorrhea and significant hyperandrogenism (hirsutism), and she desires contraception. The best option would be a combined oral contraceptive containing a low dose of ethinyl estradiol (e.g., 20 mcg), with a neutral or Nonandrogenic progestin (in this case, norethindrone acetate) (Answer B). This approach is consistent with clinical practice guidelines. Although she is 38 years old, she appears to be at low risk for adverse events. She has a low risk of cardiovascular disease and no history of migraine headaches, gallbladder disease, or personal or family history of venous thromboembolism. Her calculated 5-year risk of breast cancer is similar to that of other women her age. A levonorgestrel-releasing intrauterine device would provide contraception, and laser hair removal would benefit her hirsutism (Answer A).

9.3. ANSWER: B) However, the laser therapy would be more successful if she were also on pharmacologic therapy to suppress her androgens (a combined oral contraceptive or antiandrogen such as spironolactone). If not, she will continue to regrow terminal hairs and require frequent laser treatments. There are also reports of levonorgestrel-releasing intrauterine devices causing alopecia, particularly in women with polycystic ovary syndrome.

Spironolactone and barrier contraception (Answer E) would help her hirsutism and provide some degree of contraception but would not treat her irregular menses. This would leave her at risk for endometrial hyperplasia due to unopposed endogenous estrogen. Combined oral contraceptives with a higher dose of ethinyl estradiol (50 mcg) (Answer C) are now rarely used because they are associated with higher risks of thromboembolism and stroke. An antiandrogenic progestin, drospirenone, 4 mg daily (Answer D), would not be an optimal choice. She would likely experience unsuppressed androgen levels with ongoing androgenic symptoms.

Educational Objective: Recommend first-line treatment for a patient with multiple clinical manifestations of polycystic ovary syndrome.

10.1. A 28-year-old ♀ presents to discuss options for treating severe premenstrual dysphoric syndrome. Menarche was 12 years old and has regular menses every 28 days. Since her mid-20s, she has been experiencing mood symptoms the week before her menses. Recently, she has been unable to work 1-2 days per month because of her mood swings, irritability, and sense of hopelessness during this time. She feels better once her period starts. Her family history is notable for hypertension, diabetes, and depression.

Exam: BMI 28. the rest of the findings are normal. Which is the best option for treating this patient's premenstrual syndrome?

A. Alprazolam
B. Cyclic regimen of an estrogen-progestin oral contraceptive
C. GnRH agonist
D. Selective serotonin reuptake inhibitor
E. Tricyclic antidepressant

10.2. ANSWER: D) Selective serotonin reuptake inhibitor

Women with premenstrual syndrome experience a wide variety of cyclic and recurrent physical, emotional, behavioral, and cognitive symptoms that start in the luteal phase and diminish and stop after the onset of menses. The most severe form of premenstrual syndrome is known as premenstrual dysphoric disorder. Major symptoms include affective symptoms, such as depression, angry outbursts, irritability, and anxiety, and somatic symptoms, such as breast pain, bloating, swelling, and headache. Initiation of a selective serotonin reuptake inhibitor (Answer D) that targets mood directly is currently the treatment of choice, especially in women with premenstrual depressive symptoms, as in this case. Controlled studies confirm that abrogation of ovulation with oral contraceptives administered continuously or with a 4-day pill-free interval are also effective.

10.3. ANSWER: D) Selective serotonin reuptake inhibitor

A cyclic estrogen-progestin oral contraceptive (Answer B) refers to those with a 7-day pill-free interval. Continuous oral contraceptive pills are a reasonable treatment option; however, this was not provided as an answer option. The focus is on multimodal treatment, including cognitive behavioral therapy. Use of a GnRH agonist (Answer C) may be helpful, but this is reserved for patients unresponsive to other treatments and should include sex-steroid add-back. Tricyclic antidepressants (Answer E) have been supplanted by newer targeted drugs and are thus not the best option. Benzodiazepines, in particular alprazolam (Answer A), have been used in the past as adjunctive therapy for women with premenstrual dysphoric disorder. However, this approach is no longer used, as the risks of potential misuse outweigh the benefits.

Educational Objective: Recommend treatment options for women with premenstrual dysphoric disorder.

11.1. A 29-year-old ♀ is referred for evaluation of infertility. She and her husband have been trying to conceive for the past year. The patient reports that she always had regular monthly menstruation until several years ago when it became irregular (every 2-3 months). She has also developed night sweats that come and go. She finds them bothersome enough to seek medical attention.

Exam: BMI 22. BP: 110/70. no acne or hirsutism.

Lab: (cycle day 3): TSH 1.6 mIU/L (0.5-5). FSH 42 mIU/mL (2-12 [follicular]). LH 30 mIU/L (1-18) follicular). Prolactin 12 ng/mL (4-23). estradiol 19 pg/mL (10-180) [follicular]). Additional testing: Karyotype: 46,XX. Fragile X premutation negative. Serum adrenal cortical and 21-hydroxylase antibodies, negative. Her husband's semen analysis is normal

Which therapies is most likely to help this patient become pregnant?

A. Clomiphene citrate
B. In vitro fertilization with donor oocytes
C. GnRH agonist followed by exogenous gonadotropins
D. Letrozole therapy
E. Low-dose estradiol therapy

11.2. ANSWER: B) In vitro fertilization with donor oocytes

This woman has spontaneous primary ovarian insufficiency. Her primary ovarian insufficiency is not due to Turner syndrome, fragile X premutation, or autoimmune oophoritis. Fertility strategies for women with ovulatory infertility (without ovarian insufficiency) are ovulation induction agents. For example, women with polycystic ovary syndrome are treated with either letrozole (Answer D) or clomiphene citrate (Answer A). However, neither would work in patients with ovarian insufficiency. Low-dose estradiol therapy (Answer E), exogenous gonadotropins, and GnRH agonists followed by exogenous gonadotropins (Answer C) have all been used to induce ovulation in women with primary ovarian insufficiency, but none have been successful. One successful strategy has been in vitro fertilization with donor oocytes (Answer B). Other options include embryo donation and adoption. If this patient had Turner syndrome, a careful cardiovascular evaluation would be required before considering in vitro fertilization with donor oocytes, as death from aortic dissection has been reported during pregnancy.

Educational Objective: Recommend treatment options for women with primary ovarian insufficiency and infertility.

12.1. A 28-year-old ♀ seeks evaluation for PCOS. She has oligomenorrhea, hirsutism, and acne. Transvaginal US shows PCO morphology. She is eager to start treatment for acne and hirsutism. An estrogen-progestin contraceptive (ethinyl estradiol, 20 mcg, with norethindrone acetate, 1 mg) is prescribed. Eight months later, the patient returns for follow-up evaluation. Her acne has improved, but she reports that she has not had any bleeding during the placebo week for the past four cycles. Several Home pregnancy tests have been negative. She has not missed a single pill, and she takes no other medications. She wonders whether the pill has "stopped working."

Exam: BMI 22. Which is the best next step in this patient's management?

A. Endometrial biopsy
B. Monthly serum hCG measurements
C. Reassurance; no evaluation needed
D. Serum estradiol measurement
E. Serum prolactin measurement

12.2. ANSWER: C) Reassurance; no evaluation needed

Amenorrhea is a common occurrence in women taking certain oral contraceptives. It is due to the development of an atrophic endometrium (progestin effect). Amenorrhea eventually develops in most women on continuous preparations (hormone pills only, no placebos), but it can also occur in women using cyclic preparations, most commonly the 20-mcg pills, which are more progestin-dominant than the 30- to 35-mcg preparations. Women should be reassured that the pill is effective and that no further evaluation is needed (Answer C). As long as they have not missed pills or started medications that interfere with estrogen's metabolism, monthly pregnancy tests (Answer B) are unnecessary. Some women prefer to switch to a different preparation with a higher dosage of estrogen that is less likely to result in an atrophic endometrium in order to restore menstrual bleeding each month. Many clinicians worry that a new endocrine disorder has developed when amenorrhea occurs in this setting, but the amenorrhea reflects the endometrial response to exogenous estrogen and progestin. Thus, neither serum prolactin measurement (Answer E) nor endometrial biopsy (Answer A) is necessary.

Educational Objective: Recommend the best course of action for women who develop amenorrhea on low-dosage oral estrogen-progestin contraceptives.

13.1. A 44-year-old ♀ with a history of class III obesity presents to discuss hormonal contraception. Menarche was 13 years old, and her menstrual cycles were regular (every 28-32 days). For the past 9-12 months, her cycles have become both irregular (occurring every 2-3 months) and heavy. She has noticed night sweats right before her periods. At a recent visit to her primary care physician, her hematocrit level was 32% (0.32), and iron supplementation was initiated. She was also prescribed tirzepatide for weight loss.

Exam: BMI 40. BP: 140/90. Pulse: 80.

Which methods of contraception would be best for this patient?

A. Combined estrogen-progestin oral contraceptive with ethinyl estradiol, 20 mcg, with levonorgestrel
B. Copper intrauterine device
C. Cyclic medroxyprogesterone, 10 days/month
D. Depo-medroxyprogesterone injections
E. Levonorgestrel-releasing intrauterine device

13.2. ANSWER: E) Levonorgestrel-releasing intrauterine device

Contraceptive options for women after their childbearing years are evolving. The levonorgestrel-releasing intrauterine device (Answer E) is a good option for perimenopausal women who desire both contraception and bleeding management. In addition, it is now often used as the progestin for women taking menopausal hormone therapy. A copper intrauterine device (Answer B) would be an effective contraceptive. However, it is associated with increased menstrual bleeding, so it is not an optimal choice for this patient who is anemic. Cyclic progestin (Answer C) can help regulate menses in anovulatory women, but it does not provide contraception. In healthy nonsmoking women, low-dose (ethinyl estradiol, 20 mcg) combined oral contraceptives (Answer A) can be used until menopause. However, tirzepatide interferes with the efficacy of oral contraceptive pills. In addition, both older age and higher BMI increase the risk for venous thromboembolism, so this patient is not a good candidate for combined oral contraceptives. Depo-medroxyprogesterone injections (Answer D) are not an optimal choice because they are associated with more adverse effects (including weight gain) and complications (including bone loss) than other options.

Educational Objective: Explain the treatment options for contraception in perimenopausal women with anemia due to heavy menstruation.

14.1. A 42-year-old ♀ seeks advice for irregular menstrual cycles. She previously had 30-32-day cycles, but for the past 18 months, her menstrual periods have become unpredictable, occurring every 21-60 days. Her last menstrual period was 50 days ago. She has gained weight over the past 2-3 years, and her current BMI is 31 kg/m². She has been having difficulty sleeping and wakes frequently at night. She is very worried and would like an evaluation to determine the etiology of her symptoms

Lab: (cycle day 50): LH 15 mIU/mL (1-18 mIU/mL [follicular]). FSH 24 mIU/mL (2-12 [follicular]). Estradiol 180 pg/mL (10-180 pg/mL [follicular]). Progesterone: < 1 ng/mL (2-20 ng/mL). Which is the most likely cause of this patient's clinical picture?

A. Estradiol-secreting granulosa-cell tumor
B. Menopausal transition (perimenopause)
C. Obesity
D. Polycystic ovary syndrome
E. Pregnancy

14.2. ANSWER: B) Menopausal transition: This woman is experiencing some of the typical symptoms of the menopausal transition or perimenopause (change in menstrual cycles and new sleep disturbance, likely due to hot flashes) (Answer B). Many cycles during the transition are anovulatory, and serum estradiol levels are extremely high at times, followed by a rapid drop. FSH concentrations vary depending on estradiol levels and whether there has been recent ovulation. While testing is not indicated in women older than 45 years with typical symptoms, this patient is in the range for early menopause. Obesity alone (Answer C) can be associated with a change in menstrual cycles, but it would not explain her high serum estradiol or vasomotor symptoms. Symptoms during the menopausal transition may include breast soreness when estradiol levels are extremely high, and hot flashes/night sweats when estradiol levels fall. Serum progesterone concentrations would be much higher with pregnancy (Answer E). The high estradiol value is not enough to raise suspicion for a granulosa-cell tumor (Answer A). Women with such tumors often have abdominal pain (the tumors are large) and present with bleeding and endometrial hyperplasia.

Women with polycystic ovary syndrome (Answer D) typically have a history of irregular menses that began during adolescence. Serum LH is usually greater than FSH in women with polycystic ovary syndrome Ovarian syndrome, while this patient's picture is more consistent with ovarian insufficiency (FSH > LH).

Educational Objective:

Identify the characteristic clinical and biochemical findings of the menopausal transition.

15.1. A 46-year-old ♀ seeks evaluation for years. She had regular 28-30-day cycles until age 43, when her intermenstrual interval shortened to 24-25 days. Her cycles have become more unpredictable for the past year, occurring every 40-60 days. She experiences night sweats that interfere with sleep, particularly during the week before her menses. A recent hCG measurement was negative, and her TSH concentration was normal. She would like to know what is causing her irregular periods and night sweats. Exam: BP: 90/65. BMI 22.
Which is the most appropriate analyte to measure as the next step in this patient's evaluation?

A. A. Antimullerian hormone
B. B. FSH
C. C. Prolactin
D. D. Serum estradiol
E. E. No testing required

15.2. ANSWER: E) No testing required. Women older than 45 years who present with characteristic menopausal signs and symptoms are more likely to be in the menopausal transition than to have a new endocrine problem such as hyperprolactinemia or thyroid disease. Pregnancy must always be ruled out, but this patient's hCG was negative. Although she has no hot flashes, poor sleep and musculoskeletal symptoms are suggestive of perimenopause, as these symptoms occur in up to 40% to 50% of women during the transition While most perimenopausal women's sleep disturbances are related to hot flashes, others have poor sleep because of new-onset primary sleep disorders. Depression and anxiety can also contribute. Therefore, for women older than 45 years who present with irregular menstrual cycles and menopausal symptoms such as hot flashes, mood changes, joint aches, or sleep disturbances, biochemical evaluation or imaging is not necessary to make the diagnosis. Thus, no further testing is required (therefore, Answer E is correct and Answers A, B, C, and D are incorrect). In fact, serum FSH measurement can be misleading because it is often normal (if measured after ovulation or when serum estradiol is high). An endocrine evaluation should be performed for women younger than 45 years who present with oligomenorrhea, with or without menopausal symptoms.

Educational Objective: Guide the evaluation and diagnosis of the menopausal transition.

16.1. A 70-year-old ♀ seeks a second opinion for recent-onset hirsutism, alopecia, and vaginal bleeding. Six months ago, she noticed that her scalp hair was thinning and that she was developing hair on her chin, neck, upper lip, and stomach. She has been experiencing intrusive sexual thoughts but has not noticed a change in her voice. She is otherwise in good health and is at low surgical risk. Exam: BP: 130/85. BMI: 26. She has frontal hair recession and diffuse thinning scalp hair. She has dark hair on her neck, chin, upper lip, midsection, upper abdomen, and upper and lower back (Ferriman-Gallwey score 12). There is no acne or galactorrhea. She has clitoromegaly, with a clitoral measurement of 10 x 5 mm.
Lab: Serum total testosterone: 650 ng/dL (repeat value 700 ng/dL) (8-60). LH: 12 mIU/mL (>30), FSH: 16 mIU/mL (>30). Estradiol: 290 pg/mL (<20). DHEAS: 220 µg/dL (15-157). TSH: 2.8 mIU/L (0.5-5). Prolactin 17 ng/mL (4-30). Urinary free cortisol: 40 µg/24 h. Transvaginal US: endometrial thickness of 11 mm (normal thickness in a postmenopausal ♀ < 4-5 mm), normal-sized ovaries for age, and no masses or cysts. Endometrial biopsy reveals endometrial hyperplasia. No masses are identified on adrenal CT.
Which of the following is the best next step in this patient's management?

A. GnRH agonist therapy
B. Hysterectomy with bilateral oophorectomy
C. Measurement of serum free testosterone
D. Ovarian-adrenal venous sampling to determine the source of the androgen excess
E. Repeated imaging studies in 3 months

16.2. ANSWER: B) Hysterectomy with bilateral oophorectomy

This 70-year-old woman has severe hyperandrogenism causing virilization (clitoromegaly) and endometrial hyperplasia due to peripheral conversion of androgens to estrogen. She has an extremely high testosterone level, most likely due to an androgen-secreting ovarian or adrenal tumor. The source is likely ovarian, given the normal findings on adrenal CT and the lack of coexisting hypercortisolism. Therefore, this patient should undergo a hysterectomy with bilateral oophorectomy (Answer B). Some clinicians mistakenly assume that such a patient could be monitored with serial imaging (Answer E) if there is no visible tumor on initial studies. However, with a testosterone level this high, a normal adrenal CT scan, and no evidence of hypercortisolism, she has an ovarian tumor and needs surgery. In premenopausal women who have not completed childbearing, the goal is to identify the affected ovary and perform a unilateral oophorectomy. Ovarian venous sampling (Answer D) is a difficult procedure, and results are not Reliable (it successfully predicts the side of the rumor in only about 60% of cases). In addition, in a 70-year-old patient, the potential risk of a sampling procedure outweighs moving forward with bilateral oophorectomy.

A free testosterone concentration (Answer C) is neither necessary nor helpful.

There is no indication for GnRH agonist therapy (Answer A), which can be considered for postmenopausal ovarian hyperthecosis.

Educational Objective:

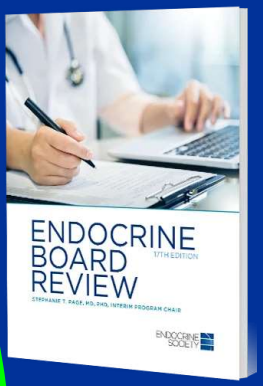
Recommends the best management option for severe postmenopausal hyperandrogenism.

مراجعات البورد في الغدد

EBR.17

Male Reproduction

M. Reproduction



الدكتور محمد الشعباني

1.1. A 55-year-old man is referred for treatment of male hypogonadism. He describes decreased libido over the past year, reduced performance in his regular weekly jogs, and overall decreased energy. He is married and reports his wife has also noted his decreased interest in sex. He has normal erectile function. His medical history is unremarkable except for marked eczema. Exam: BMI 29. with some central adiposity. BP: 129/78, Pulse: 70. Strength is 5/5 in all extremities. He has normal male-pattern hair and no gynecomastia. His skin is dry with some areas of irritation. Testes are 20 cc bilaterally. Lab: (AM fasting): Total testosterone: 200 ng/dL (300-900). Repeated total Testosterone: 185 ng/dL. Free testosterone (calculated): 7.8 ng/dL (9-30 ng/dL). LH: 4 mIU/mL (1-0 mIU/mL). FSH 5 mIU/mL (1-13). Hematocrit 48% (41-51%). PSA: 1.5 ng/dL (<3.8). He is counseled regarding the risks and benefits of testosterone therapy, and he elects to initiate a trial of testosterone. To accommodate his preference for oral delivery, oral testosterone undecanoate is prescribed. He returns in 3 months and has noted a mild increase in his libido, but his energy remains poor and there is no increase in muscle mass or stamina. His trough testosterone concentration 12 hours after his last dose is 185 ng/dL (6.4 nmol/L), and his hematocrit is 49% (0.49). He states that he is adhering to his testosterone treatment regimen and takes it first thing in the morning on an empty stomach and with dinner.

Which is the best strategy to optimize his hypogonadism treatment?

A. Discontinue testosterone as he is not benefiting
B. Increase the dosage of oral testosterone undecanoate
C. Remind him to take oral testosterone undecanoate with a fatty meal
D. Switch to oral methyltestosterone
E. Switch to weekly testosterone enanthate injections

1.2. ANSWER: C) Remind him to take oral testosterone undecanoate with a fatty meal: Oral testosterone undecanoate has been approved for the treatment of male hypogonadism in the United States for more than 5 years and in Europe for much longer. Oral testosterone undecanoate is preferred by some men who dislike transdermal gels and injections. This formulation must be taken twice daily and, importantly, requires ingestion of a fatty meal (Answer C) to maximize absorption, as oral testosterone undecanoate is primarily absorbed via the lymphatics. This patient takes his first dose of the day on an empty stomach, and he is thus very unlikely to be experiencing eugonadal testosterone levels throughout the day. Before switching methods (Answer E) or increasing his dosage (Answer B), he should be instructed regarding the optimal use of his current therapy and retrialed for clinical benefit Ultimately, discontinuing testosterone therapy (Answer A) may be considered, but at this juncture, he has not yet optimized therapy to assess benefit.

Although oral methyltestosterone (Answer D) has been approved for decades, it is associated with liver toxicity and should not be used to treat male hypogonadism.

Educational Objective:

Explain the pharmacokinetics of oral testosterone.

2.1. A 56-year-old ♂ with a history of hypertension and hyperlipidemia is referred for low testosterone following hospital discharge 1 week ago. During his recent hospitalization, he had placement of 3 cardiac stents following a non-ST-segment elevation myocardial infarction. He is initiating cardiac rehabilitation next week. He has a 2-year history of erectile dysfunction. He has gained approximately 40 lb (18.1 kg) over that same period. During his hospitalization, he was noted to have a morning fasting total testosterone concentration of 180 ng/dL (SI: 6.2 nmol/L). Exam: findings are notable for BMI 38 and central adiposity. He has normal male-pattern hair with some balding and normal findings on genitourinary exam with 15-cc testes bilaterally Lab: (8 AM): Total testosterone 250 ng/dL (300-900). Free testosterone (calculated) 8 ng/dL (9-30 ng/dL). Estradiol 40 pg/mL (10-40). LH 3 mIU/mL (1-9).

Which is the best next step in managing this patient's erectile dysfunction?

A. Initiate an aromatase inhibitor
B. Initiate long-acting testosterone undecanoate injections
C. Initiate testosterone transdermal gel
D. Refer him to a sex therapist
E. Repeat laboratory assessment following cardiac rehabilitation

2.2. ANSWER: E) Repeat laboratory assessment following cardiac rehabilitation

This patient has nonspecific symptoms that possibly reflect central hypogonadism. However, he has had an acute health event. During acute illness, the hypothalamic-pituitary-gonadal axis is suppressed, and thus it is not the appropriate time to evaluate for hypogonadism. Moreover, his hypothalamic-pituitary-gonadal axis may be recovering, with an increase in testosterone since hospitalization. Therefore, before instituting testosterone replacement (Answers B and C), he should have confirmatory biochemical testing once he has fully recovered from his hospitalization and cardiac event (Answer E). Although his estradiol concentration is at the upper end of the reference range, likely due to peripheral aromatization in adipose tissue, first-line therapy for testosterone deficiency (if indeed this is diagnosed with confirmatory testing following cardiac rehabilitation) would be testosterone replacement, not an aromatase inhibitor (Answer A). Aromatase inhibitors Only mildly increases serum testosterone and can adversely affect long-term bone health.

While he may benefit from counseling with a sex therapist (Answer D), this patient has symptoms that may be related to hypogonadism and he should be properly evaluated after recovery. In addition, findings from the TRAVERSE trial have been reassuring regarding the safety of testosterone replacement therapy in men with established cardiovascular disease. Of note, the TRAVERSE study included men who were at least 6 months out from their cardiac event, which aligns with current recommendations regarding therapy initiation.

Educational Objective: Determine when to evaluate the hypothalamic-pituitary-gonadal axis following an acute health event.

3.1. A 40-year-old ♂ with HIV is referred for evaluation of low testosterone. He has fatigue and describes a recent decrease in libido with normal erectile function. He is on highly active antiretroviral therapy (HAART) and has an undetectable viral load.
Exam: he is a thin man in no apparent distress. BMI 21. He has no gynecomastia or galactorrhea. Genitourinary exam: normal, with 15-cc testes bilaterally.
Lab: (8 AM): Total testosterone: 270 ng/dL (300-900). Free testosterone: 7.8 ng/dL (9-30). Repeat lab: Total testosterone: 250 ng/dL. Free testosterone: 7.2 ng/dL. FSH: 3 mIU/mL (1-13).
LH 2 mIU/mL (1-9). PSA 1 ng/mL (< 2). Prolactin 14 ng/mL (4-23). Hemoglobin 13.1 g/dL (13.8-17.2).
Hematocrit 39% (41-51%). TSH: 4.2 mIU/L (0.5-5). FT4: 0.7 ng/dL (0.8-1.8).
Which is the best next step in addressing this man's fatigue?

A. Initiate cabergoline
B. Initiate levothyroxine
C. Initiate testosterone transdermal gel
D. Order iron studies to evaluate anemia
E. Perform pituitary MRI

3.2. ANSWER: E) Perform pituitary MRI: This patient has new-onset, symptomatic secondary hypogonadism with inappropriately low gonadotropin concentrations for his level of serum free testosterone. Free testosterone is a better measure of biochemical hypogonadism in men on highly active antiretroviral therapy (HAART), as HAART raises serum SHBG. In men younger than 50 years who have new-onset central hypogonadism, a pituitary MRI (Answer E) is warranted to rule out a pituitary adenoma despite normal thyroid function. Initiation of cabergoline (Answer A) without confirmatory MRI may miss a nonfunctional pituitary adenoma. Moreover, his prolactin is not high enough to ascribe his hypogonadism to a prolactinoma without further evaluation. While it would not be wrong to order iron studies to evaluate anemia (Answer D), this would not address his hypogonadism and might miss a growing pituitary mass. Similarly, managing his borderline hypothyroidism (Answer B) would not address hypogonadism. Initiating testosterone therapy (Answer C) would not be appropriate without determining the etiology of his hypogonadism, which may require further intervention.

Educational Objective:

Select patients to refer for pituitary imaging in the evaluation of hypogonadism.

4.1. A 32-year-old ♂ describes fatigue, a weight gain of 18 kg in the last 4 years, and decreased sexual performance. He states, "I don't take very good care of myself as I don't have time to exercise or eat properly due to long hours at work." He and his wife would like to start a family in the coming years, and his change in sexual performance worries him. He is usually able to maintain an erection for intercourse. He has recently noted a decrease in libido. His only medications are atorvastatin, 80 mg/day, for hyperlipidemia and hydrochlorothiazide for hypertension. He has sleep apnea and uses continuous positive airway pressure most nights. Exam: BMI 41 with marked central adiposity, and normal findings on genitourinary exam with 20-cc testes bilaterally.
Lab: Total testosterone (8 AM) (by liquid chromatography/tandem mass spectrometry) = 280 ng/dL (300-900 ng/dL). Repeat total testosterone (8 AM) = 290 ng/dL. LH: 4 mIU/mL (1-9). FSH: 3 mIU/mL (1-13). Prolactin 4 ng/ml (4-23). Hematocrit 48% (41-50%).
He has seen television ads about low testosterone syndrome and would like to start testosterone, as he has heard it will help him lose weight and improve his energy and sexual performance. Which is the best next step for managing this patient's concerns?

A. Advise him to stop atorvastatin while they are trying to conceive
B. Initiate a GLP-1 receptor agonist and encourage lifestyle modifications
C. Initiate a 3-month trial of transdermal testosterone gel
D. Initiate clomiphene citrate
E. Initiate recombinant hCG therapy

4.2. ANSWER: B) Initiate a GLP-1 receptor modifications: This patient has nonspecific symptoms of hypogonadism and clinically significant obesity. He has borderline-low testosterone levels, but given his obesity, his free testosterone concentration is likely well within the reference range (obesity decreases SHBG). Weight loss can significantly increase serum testosterone, and recent data suggest that weight loss induced by GLP-1 receptor agonists (Answer B) increases serum testosterone, similar to the weight loss achieved through lifestyle changes and bariatric surgery. Initiation of testosterone therapy (Answer C) is inappropriate in a patient with normal testosterone concentrations. Furthermore, exogenous testosterone inhibits spermatogenesis by interrupting the hypothalamic-pituitary-gonadal axis, suppressing LH, FSH, and intratesticular Testosterone production, a strategy used in the development of male hormonal contraceptives. Initiation of hCG therapy (Answer E), while it would preserve fertility, is incorrect because he does not have hypogonadism. Initiation of clomiphene citrate (Answer D) could raise serum testosterone, but he does not have hypogonadism or known abnormalities in sperm production. Despite their impact on cholesterol, high-dosage statins do not significantly lower serum testosterone concentrations, so recommending that he discontinue this medication (Answer A) is incorrect. While statins are contraindicated in women who are trying to conceive because they are teratogenic, particularly in the first trimester, no such effects have been reported in fathers taking statins.
Educational Objective: Interpret testosterone values in men with obesity and explain how weight loss can raise serum testosterone levels.

5.1. A 72-year-old ♂is referred for treatment of low testosterone that was documented following a wrist fracture. He has a history of cardiovascular disease (1 stent), hyperlipidemia treated with atorvastatin, depression, and T2D treated with metformin and liraglutide. He describes a gradual decrease in libido and memory over the last several years. His referring provider has ordered a DXA, and he is noted to have a T-score of -2.6 at the hip.

Lab: Total testosterone: 239 ng/dL (300-900). Free testosterone 7.5 ng/dL (9-30). HbA1c: 7.7% (4-5.6%) (61 mmol/mol). Repeat lab: (8 AM): Total testosterone 220 ng/dL (300-900). Free testosterone: 7.4 ng/dL (9-30). FSH 5 mIU/mL (1-13). LH 4.1 mIU/mL (1-9). PSA 2.3 ng/mL (<5.3). Hematocrit 39% (41-51%). Transdermal testosterone therapy is initiated.

According to the latest randomized controlled trials, which of the following is expected to improve if this patient starts testosterone replacement therapy?

A. Anemia
B. Cognition
C. Risk of future cardiovascular events
D. Risk of future fractures

5.2. ANSWER: A) Anemia: The double-blinded, randomized controlled Testosterone Trials (T-Trials) provide the most definitive data to date regarding the benefits of testosterone therapy in older men with low testosterone and at least one symptom of hypogonadism. The study population was symptomatic men older than 65 years who had a total testosterone concentration less than 275 ng/dL (<9.5 mmol/L). Participants randomly assigned to testosterone therapy had increased total testosterone and improvements in sexual activity and libido; mild improvements in mood and reduced severity of depressive symptoms; and improvements in physical function as assessed by a 6-minute walk test. Importantly, in participants with unexplained anemia, those receiving testosterone had a clinically significant increase in hemoglobin (thus, Answer A is correct).

5.3. ANSWER: A) Anemia:

While testosterone therapy increases bone mineral density and may increase bone strength (effects observed in the T-Trials and other studies), no randomized controlled trials of testosterone therapy have been powered to address fracture risk. Importantly, recent reports from the TRAVERSE study have not supported a benefit of testosterone therapy in preventing fracture (Answer D) and, in fact, have suggested there may be an increased fracture risk associated with testosterone treatment. Testosterone therapy does not reproducibly improve mental cognition in men (Answer B), an effect that was also not observed in the "Vitality" substudy nested within the T-Trials or in the cognition assessment (HIS-Q) in the TRAVERSE trial.

5.4. ANSWER: A) Anemia:

The TRAVERSE study, a noninferiority trial in men at high risk for cardiovascular disease, demonstrated no significant increase or decrease in cardiovascular disease events (Answer C) with testosterone therapy compared with placebo. While the T-Trials were not powered to assess cardiovascular risk with testosterone therapy, no difference in cardiovascular events was seen compared with placebo

Educational Objective: Explain the current evidence regarding the risks and benefits of testosterone therapy in older men with symptomatic, late-onset hypogonadism.

6.1. Primary Care physician interpreting the hormone profile of a 31-year-old ♂ who is being evaluated for infertility. He and his 28-year-old wife have been trying to conceive for 12 months and regularly have unprotected intercourse. His wife has regular menstrual cycles. He takes no medications, is a nonsmoker, and works out regularly at his local gym.

Exam: he is a healthy, muscular man with normal male-pattern hair. Genitourinary exam findings are notable for a normal phallus and 10-cc testes bilaterally without masses. Vas deferens are palpable bilaterally.

Lab: TSH: 0.8 mIU/L (0.5-5). Total testosterone: 950 ng/dL (300-900). Estradiol 15 pg/mL (4-40). LH 2 mIU/mL (1-9). FSH 2 mIU/mL (1-13). HDL: 30 mg/dL (>60). Seminal fluid analyses: Total semen volume 2 Ml. Sperm concentration 1 million/mL (oligospermia). Which regimens best explains this patient's hormone profile and seminal fluid analyses?

A. Androgenic anabolic steroid plus an aromatase inhibitor
B. Desiccated thyroid and DHEA
C. Exogenous hCG
D. 5a-Reductase inhibitor
E. Testosterone plus an aromatase inhibitor

6.2. ANSWER: E) Testosterone plus an aromatase inhibitor

This patient's infertility is due to oligospermia, likely the result of exogenous androgen use. Exogenous androgens (including testosterone and anabolic steroids) suppress spermatogenesis by interrupting the hypothalamic-pituitary-gonadal axis, which suppresses endogenous testosterone production.

Over time, exogenous androgens result in reversible reductions in testicular size, as in this patient.

This patient's estradiol concentration is low in the presence of high testosterone, which serves as the substrate for aromatase, and this suggests that he is taking an aromatase inhibitor. The fact that his testosterone concentration is high rules out the possibility that he is taking an anabolic steroid (Answer A) because anabolic steroids are not detected in modern testosterone assays.

6.3. ANSWER: E) Testosterone plus an aromatase inhibitor

While modest reductions in HDL cholesterol. This can be seen with testosterone administration. Non-aromatizable anabolic androgens profoundly suppress HDL cholesterol, which is not observed here. His hormone profile and oligospermia are best explained by testosterone plus an aromatase inhibitor (Answer E). Exogenous testosterone, hCG, and anabolic steroids all suppress gonadotropins, so the degree of gonadotropin suppression does not help differentiate between the hormone regimens. hCG increases serum testosterone, which in turn is aromatized to estradiol. Thus, exogenous hCG (Answer C) would raise both serum estradiol and testosterone concentrations, which is not the case here.

6.4. ANSWER: E) Testosterone plus an aromatase inhibitor

Exogenous thyroid might mildly suppress TSH, but exogenous DHEA (Answer B) does not increase testosterone or profoundly suppress gonadotropins. 5α-Reductase inhibitors (Answer D) can mildly increase serum testosterone, but estradiol would be expected to increase in conjunction with testosterone, and profound gonadotropin suppression is not observed with 5α-reductase inhibitors.

Educational Objective:

Highlight the reproductive and hormonal changes associated with testosterone and androgenic anabolic steroid use.

7.1. A 28-year-old transgender ♂ is referred for initiation of gender-affirming hormone therapy. During the appointment, treatment goals and expectations are reviewed, along with the risks and benefits of therapy and the potential impact on future fertility. BMI: 30. There is no history of hypertension, dyslipidemia, T2D, or venous thromboembolism. Testosterone cypionate, 100 mg/IM/week, is prescribed. Which clinical changes is he most likely to see in the first 6 months of hormone therapy?

A. Decrease in breast size
B. Deepening of the voice
C. Increased muscle strength
D. Weight loss

7.2. ANSWER: A) Acne

After starting testosterone therapy, this transgender man can anticipate masculinizing effects (e.g., voice deepening [Answer C] and increased muscle strength [Answer D]), many of which are not apparent until after 6 to 12 months of therapy. In contrast, an increase in oily skin and Sometimes acne (Answer A) can occur within the first 6 months of treatment. Androgen administration is associated with an increase in lean body mass and body weight, not weight loss (Answer E). Testosterone therapy may eventually result in a decrease in glandular tissue (Answer B), but this is not an early effect of androgen administration.

Educational Objective:

Identify the early masculinizing features of gender-affirming hormone therapy in transgender men.

8.1. A 67-year-old ♂ seeks evaluation for inability to ejaculate. He reports a normal libido and is sexually active with his wife. He has noticed that it takes a little longer to get an erection than in the past, but he can still get and maintain an erection that is adequate for intercourse. He generally reaches orgasm but is concerned that there is no longer an ejaculation. His history is notable for hypertension and benign prostatic hyperplasia, for which he takes hydrochlorothiazide, 12.5 mg daily, and tamsulosin, 0.4 mg daily.
Exam: BMI 31. BP: 125/80. He is well Virilized, and testes are 15 cc bilaterally. Rectal exam reveals mild prostate enlargement. His morning testosterone concentration is 345 ng/dL. Which strategies is most likely to help his ejaculatory dysfunction?

A. Refer him to urology for transurethral resection of the prostate
B. Start a phosphodiesterase-5 inhibitor
C. Start testosterone replacement
D. Substitute dutasteride for tamsulosin
E. Substitute spironolactone for hydrochlorothiazide

8.2. ANSWER: D) Substitute dutasteride for tamsulosin

Ejaculation is the discharge of semen from the male reproductive tract, usually accompanied by orgasm. Retrograde ejaculation occurs when semen, which would normally be ejaculated via the urethra, is instead redirected to the bladder. Normally, the bladder sphincter contracts before ejaculation, which acts to both inhibit the release of urine and prevent a reflux of seminal fluids into the bladder during ejaculation. Any condition, medication, or surgical procedure that interferes with central control of ejaculation or the autonomic innervation to the seminal tract can cause ejaculatory dysfunction. Use of a-adrenergic blockers, such as tamsulosin, to treat symptoms of benign prostatic hyperplasia is a common cause of retrograde ejaculation given that they relax the bladder sphincter. Other drug classes used to treat benign prostatic hyperplasia, such as saline reductase inhibitors, do not have this adverse effect, so substituting dutasteride for tamsulosin (Answer D) would be a helpful strategy for this patient.

8.3. ANSWER: D) Substitute dutasteride for tamsulosin

While cross-sectional studies show an association between low testosterone levels and ejaculatory dysfunction, testosterone replacement (Answer C) has not been shown to be beneficial in such patients. In any case, this patient does not meet criteria for hypogonadism given that his testosterone concentration is in the normal range. This patient can obtain and maintain an erection adequate for intercourse, and phosphodiesterase-5 inhibitors have no effect on ejaculatory function. Therefore, initiating treatment with a phosphodiesterase-5 inhibitor (Answer B) would not be helpful. In addition, an agent such as tadalafil can interact with tamsulosin and result in hypotension. Surgical treatment of benign prostatic hyperplasia (Answer A) is not indicated for the treatment of retrograde ejaculation

8.4. ANSWER: D) Substitute dutasteride for tamsulosin

Retrograde ejaculation is not uncommon following surgery for benign prostatic hyperplasia. A diuretic might not be an ideal choice for a patient with benign prostatic hyperplasia. Nonetheless, hydrochlorothiazide is a safe, effective, and inexpensive agent that is doing a good job controlling this patient's blood pressure at a low dosage. While it may contribute to erectile dysfunction, it does not cause ejaculatory dysfunction. Therefore, substituting spironolactone for hydrochlorothiazide (Answer E) is not indicated, as it would not be expected to provide any additional benefit and could cause gynecomastia.

Educational Objective:

Explain the association between the use of alpha-adrenergic blockers and retrograde ejaculation

9.1. A 36-year-old ♂ with Klinefelter syndrome is referred for ongoing care. He has been on testosterone cypionate injections, 200 mg every 2 weeks, for 5 years to treat hypogonadism. He takes lisinopril, 10 mg daily, for hypertension and oxycodone, 30 mg daily, for chronic back pain following a car accident. He is married and has no children. He has had diminished libido over the last 2 years, and unwanted breast tissue has developed in the last 2 months

Exam: he is a tall, slender man with mild central adiposity. BP: 145/90. Pulse: 80. BMI: 28. His skin is clear except for mild acne on his back, and he has normal male-pattern facial hair with a thin beard. He has scant chest hair and a nontender, firm, and immobile 2-cm gynecomastia on the right side and a nontender 1-cm gynecomastia on the left side. Testes are 10 cc bilaterally.

Lab: (midway between scheduled testosterone injections): Testosterone: 400 ng/dL (300-900). Estradiol: 50 pg/mL (10-40). LH 2 mIU/mL (1-9). FSH: 3 mIU/mL (1-13). Hematocrit 48% (41-51%). Which is the most appropriate next step in the management of this patient's gynecomastia?

A. Add anastrozole, 1 mg daily
B. Consult with his pain specialist to decrease his oxycodone dosage
C. Increase the testosterone injection dosage to 250 mg every 2 weeks
D. Refer for mammography
E. Switch to transdermal 1% testosterone gel, 50 mg daily

9.2. ANSWER: D) Refer for mammography:

Individuals with Klinefelter syndrome have a greater than 20-fold increased risk for breast cancer and a greater than 50-fold increased risk for breast cancer mortality. In addition, on physical examination, this patient has findings that should raise suspicion for malignancy, including more breast tissue on one side and immobility of the right-sided mass. The more acute course of his gynecomastia also signals that further imaging (i.e., mammography [Answer D]) is indicated. This patient's mid-injection testosterone concentration is on the low end, but it is not below the lower limit of the reference range. Attributing his gynecomastia to hypogonadism is incorrect. Thus, increasing his testosterone dosage (Answer C) or switching to transdermal delivery (Answer E) is unlikely to improve his gynecomastia or libido.

9.3. ANSWER: D) Refer for mammography:

His estradiol concentration is slightly above normal, but treatment with anastrozole (Answer A) is inappropriate given his physical examination findings and the long-term risk to his bone health. While long-term opioid use can cause secondary hypogonadism and lead to gynecomastia due to low testosterone, this patient is on testosterone replacement, and thus reducing his pain medication dosage (Answer B) is unlikely to improve gynecomastia.

Educational Objective: Identify elements of the medical history and physical examination that increase the risk of male breast cancer and require further evaluation.

10. A 29-year-old ♂ is referred for treatment of infertility. He and his wife have been having regular intercourse for 1 year, and she has normal menstrual cycles. His referring provider obtained a semen analysis documenting azoospermia. He completed chemotherapy with cyclophosphamide for Hodgkin lymphoma 4 years ago and is in remission. He reports normal energy levels and libido, has no difficulty getting or maintaining an erection, and is virilized on examination with 15-cc testes bilaterally. Which of the following hormone profiles is most likely in this patient?

Answer	Testosterone	LH	FSH
A	Normal	Normal	Normale
B	Normal	Normal/high	High
C	Low	Low	Low
D	low	High	High

10.2. ANSWER: B) Normal testosterone, 10 normal/high, high FSH

One of the most common long-term adverse effects of chemotherapy in men is gonadal dysfunction. After 1 year of follow-up, azoospermia is seen in 90% of men with Hodgkin lymphoma who have received more than 3 courses of an alkylating agent, such as cyclophosphamide. Therefore, all men about to undergo gonadotoxic chemotherapy should be offered the option of sperm cryopreservation

In the testis, the cells within the seminiferous tubules of the germinal epithelium have the highest mitotic and meiotic indices and are thus most susceptible to the toxic effects of chemotherapy. Damage to the seminiferous tubules decreases secretion of inhibin B from Sertoli cells. This drop in inhibin B, which is the major nonsteroidal regulator of FSH, leads to a 5- to 10-fold increase in FSH levels.

10.3. ANSWER: B) Normal testosterone, 10 normal/high, high FSH

By contrast, Leydig cells are less sensitive than the germinal epithelium to the gonadal toxicity of chemotherapeutic agents, which is why LH and testosterone levels are typically maintained within the normal range. In some situations, there may be evidence of subclinical Leydig-cell dysfunction, characterized by testosterone levels that are at the lower end of the normal range in association with elevated LH levels Based on this differential sensitivity of cells in the testes to chemotherapy, the typical hormone profile of a patient with azoospermia following cyclophosphamide is that of normal testosterone, normal LH, and high FSH (Answer B). Answer A is incorrect because in the setting of azoospermia, testosterone and LH levels are typically normal, but FSH would be elevated.

10.4. ANSWER: B)

Answer C depicts the hormone milieu of hypogonadotropic hypogonadism, which is what one would see Following toxicity to the hypothalamus or pituitary rather than the testis. Answer D is consistent with primary hypogonadism, but he has no symptoms of testosterone deficiency, is well virilized, and is 3 years out of his treatment. The long-term reproductive effects of cyclophosphamide are confined to the germ cells.

Educational Objective:

Explain the effect of cytotoxic chemotherapy on gonadal function and fertility in men.

11. A 35-year-old ♂ is referred for evaluation of infertility. The patient and his 32-year-old wife have not conceived after 12 months of regular, unprotected intercourse. He reports normal libido and erections. He takes no medications or recreational drugs. He goes to the gym 5 times per week. His wife has a 4-year-old daughter from a previous relationship and is ovulating according to basal body temperature measurements.

Exam: he has normal secondary sexual characteristics, no gynecomastia, and a muscular build. Testes are 20 cc bilaterally.

Lab: Total testosterone 650 ng/dL (300-900). FSH 4.4 mIU/mL (1-13). LH 6.1 mIU/mL (1-9). Seminal fluid analysis: Volume 1.3 mL (>1.5 mL) pH = 6.8 (>7.2)

No sperm are present. A repeated analysis confirms azoospermia.

Which is the most likely cause of this patient's infertility?

A. Anabolic steroid use
B. Congenital bilateral absence of the vas deferens
C. C. Mosaic Klinefelter syndrome
D. Exogenous testosterone use
E. Y-chromosome microdeletions

11.2. ANSWER: B) Congenital bilateral absence of the vas deferens

This couple's infertility is due to azoospermia. Absence of sperm in the ejaculate may occur because of an obstruction in the reproductive tract (obstructive azoospermia) or inadequate sperm production (nonobstructive azoospermia). The volume and pH of the seminal fluid can be used to categorize a patient's azoospermia. In this case, low volume and low pH indicate an obstructive etiology. Obstructive azoospermia may be congenital (congenital absence of the vas deferens, idiopathic epididymal obstruction) or acquired (from infections, vasectomy, or other iatrogenic injuries to the male reproductive tract).

Congenital bilateral absence of the vas deferens (Answer B) is one of the most common causes of obstructive azoospermia. It can be diagnosed by a careful clinical examination, as the vas is normally palpable as a thin rope-like structure within the spermatic cord.

11.3. ANSWER: B) Congenital bilateral absence of the vas deferens

The diagnosis can be confirmed by transrectal ultrasonography. Genetic testing should be performed in patients with congenital bilateral absence of the vas deferens who do not have the typical pulmonary and pancreatic manifestations of cystic fibrosis, as it is associated with compound heterozygosity for a classic (severe) CFTR pathogenic variant and a mild CFTR pathogenic variant.

The other answer options cause nonobstructive azoospermia, in which case testicular volume would be reduced because the bulk of the testis is composed of seminiferous tubules. If this patient's azoospermia were due to anabolic steroid use (Answer A), testosterone and gonadotropin levels would be suppressed. Similarly, if he were taking exogenous testosterone (Answer D), LH and FSH levels would be suppressed.

11.4. ANSWER: B) Congenital bilateral absence of the vas deferens

Y-chromosome microdeletions (Answer E) are an important cause of nonobstructive azoospermia and typically result in reduced testicular size due to disruption of spermatogenesis and an elevated FSH level. The male-specific region on the long arm of the Y chromosome has a locus known as the azoospermia factor (AZF) that contains genes needed for spermatogenesis. This AZF locus contains three regions: AZFa, AZFb, and AZFc Deletions of the entire AZFa region result in complete atrophy of the tubular compartment, with only Sertoli cells seen on testicular biopsy, making sperm retrieval for intracytoplasmic sperm injection virtually impossible. Large deletions in the AZFb region also result in Sertoli-cell-only syndrome. Pathogenic variants in the AZFc region are the most common and account for 80% of Y-chromosome microdeletions.

11.5. ANSWER: B)

AZFc deletions are compatible with residual spermatogenesis, with oligospermia being a common presentation. Patients with mosaic Klinefelter syndrome (Answer C) can present with infertility, but the patient's completely normal hormone profile, absence of gynecomastia, normal testicular size, and semen characteristics are not consistent with this diagnosis.

Educational Objective:

Diagnose obstructive azoospermia due to the absence of the vas deferens as a cause of infertility

12.1. A 74-year-old ♂ is referred for further management of hypogonadism diagnosed when he presented with decreased stamina and libido. At baseline, he had two morning testosterone values in the hypogonadal range (180 and 205 ng/dL [6.2 and 7.1 nmol/L]) and a hematocrit measurement of 50% (0.50). He has received injections of testosterone cypionate, 200 mg every 2 weeks, for the past six months. His libido has improved on this regimen, but he continues to feel tired and often takes an afternoon nap. He quit smoking cigarettes five years ago

Exam: BMI: 36. He is well virilized and has normal findings on testicular examination. His lungs are clear to auscultation.

Testosterone measured midway between injections is 420 ng/dL (14.6 nmol/L), and hematocrit is now 54% (0.54). Which is the best next step in this patient's management?

A. Arrange for monthly phlebotomy
B. Decrease his testosterone dosage to 100 mg every 2 weeks
C. Increase his testosterone dosage to 250 mg every 2 weeks
D. Schedule a sleep study
E. Switch from testosterone cypionate to long-acting testosterone undecanoate injections

12.2. ANSWER: D) Schedule a sleep study.

Testosterone esters, including enanthate and cypionate, have been used to treat male hypogonadism for more than 7 decades. They have the advantage of being the least expensive of the testosterone replacement modalities, and they predictably restore testosterone levels to the normal range However, they have unfavorable pharmacokinetics characterized by significant fluctuations in serum testosterone between peak and trough values. When administered by deep intramuscular injection, testosterone is slowly released from this oily suspension into the circulation over a period of weeks. The esters are typically injected at two-week intervals, with levels reaching peak concentrations 24 to 48 hours after the injection, followed by a gradual decline to the low-normal range before the next injection

12.3. ANSWER: D) Schedule a sleep study.

When the interval between injections is extended to every three weeks, peak concentrations tend to be supraphysiological, and testosterone levels may fall to the hypogonadal range by the time the next injection is administered. Such wide variations in serum testosterone concentrations can, in turn, cause undesirable swings in mood, libido, and energy levels. Given the pharmacokinetics of testosterone esters, they also tend to increase hematocrit more than transdermal testosterone preparations, especially when high dosages are given at less frequent intervals.

Increasing the testosterone dosage (Answer C) would be inappropriate in a patient whose hematocrit is already high, especially given that his testosterone concentration is in the normal range for midcycle.

12.4. ANSWER: D) Schedule a sleep study.

Markedly decreasing his testosterone dosage (Answer B) would probably render him hypogonadal throughout much of his dosing period and thus is unlikely to treat his symptoms of hypogonadism The pharmacokinetics of testosterone undecanoate, which requires a larger-volume injection but reduces the injection frequency to every 10 weeks after a loading dose, mean that these longer-acting injections carry a slightly reduced risk of polycythemia compared with shorter-acting esters, which produce frequent peaks. However, switching to long-acting testosterone injections (Answer E) is unlikely to address his problem of daytime sleepiness and may be insufficient to improve polycythemia. Moreover, once injected, long-acting testosterone undecanoate is not reversible and will thus continue to stimulate erythropoiesis for many weeks.

12.5. ANSWER: D) Schedule a sleep study.

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12.5. ANSWER: D) Schedule a sleep study.

Before initiating testosterone therapy, baseline hematocrit should be measured. A baseline hematocrit greater than 48% (and greater than 50% for men living at higher altitudes) is a relative contraindication to testosterone therapy because these men are more likely to develop a hematocrit level greater than 54% when treated. A baseline hematocrit of 50% is high for this hypogonadal, nonsmoking patient. The Endocrine Society clinical practice guidelines recommend investigating the underlying cause of erythrocytosis before androgen therapy is prescribed. Given the patient's obesity and history of daytime somnolence, the possibility of obstructive sleep apnea should be considered, and a sleep study should be arranged (Answer D). Occasionally, phlebotomy (Answer A) may be necessary to continue testosterone therapy in a hypogonadal patient, but it is important to rule out other causes of erythrocytosis, such as sleep apnea, chronic obstructive pulmonary disease, or polycythemia vera, before doing so.

Educational Objective: Describe the pharmacokinetics of injectable testosterone esters and manage potential adverse effects

13.1. A 19-year-old ♂ is referred because of a lack of secondary sex characteristics and small testes. His growth followed the 50th percentile throughout childhood, but he did not experience a growth spurt during his teenage years. His height is now at the 25th percentile. He has a normal sense of smell. He does not take any prescribed medications. His father, who accompanies him, reports that he himself was also a late bloomer but then developed fully and had no problems with fertility

Exam: height 168 cm, arm span 175 cm, BMI 22. He has slight axillary hair and Tanner stage 2 pubic hair but no facial or chest hair. He has no gynecomastia. His testes measure 4 cc bilaterally. Visual fields are full to confrontation.

Lab: (8 AM): Total testosterone: 50 ng/dL (300-900). FT4: 1.3 ng/dL (0.8-1.8). LH <0.2 mIU/mL (1-9). FSH: 0.3 mIU/mL (1-13). Prolactin: 10 ng/mL (4-18). Cortisol: 20 µg/dL (5-25). IGF1: low-normal for age and sex

Which of the following is the most likely diagnosis?

A. Congenital hypogonadotropic hypogonadism
B. Constitutional delay of growth and puberty
C. Pathogenic variant in the POUIFI gene
D. Pathogenic variant in the PROPI gene

13.2. Answer A) Congenital hypogonadotropic hypogonadism

This patient had prepubertal onset of hypogonadism as evidenced by a lack of secondary sexual characteristics, no increase in testicular size, and eunuchoidal proportions (arm span >5 cm greater than height). Laboratory tests show profound secondary hypogonadism with otherwise normal pituitary function and prolactin level. His presentation is thus consistent with congenital hypogonadotropic hypogonadism (Answer A). Distinguishing between constitutional delay of growth and puberty (Answer B) and congenital hypogonadotropic hypogonadism can be challenging in younger adolescent boys. The fact that this patient's father was a late bloomer might lead one to suspect constitutional delay of growth and puberty.

13.3. Answer A) Congenital hypogonadotropic hypogonadism

However, the absence of any pubertal signs by age 18 years, by definition, rules this out. It is important to recognize that delayed, but otherwise normal, puberty is seen in up to 12% of families with congenital hypogonadotropic hypogonadism. Pathogenic variants in the PROPI gene (Answer D) are one of the most common causes of both familial and sporadic congenital combined pituitary hormone deficiency (GH, TSH, LH, FSH). Thus, the fact that the patient's pituitary hormone profile is normal apart from gonadotropin deficiency rules out an abnormality in PROPI. Similarly, pathogenic variants in the POUIFI gene (Answer C), which were first described in 1992, cause combined pituitary hormone deficiency and are associated with GH, prolactin, and TSH deficiencies, with variable pituitary hypoplasia. Deficiencies of GH and prolactin are generally complete, but TSH deficiency is more variable. Gonadotropin deficiency is not seen in individuals with POUIFI pathogenic variants, so it would not explain this patient's phenotype.

Educational Objective:

Construct the differential diagnosis of a patient with prepubertal onset of hypogonadism

14.1. A 62-year-old ♂ with a 10-year history of T2D seeks help for erectile dysfunction. He reports normal libido. He has hypertension and dyslipidemia. He takes lisinopril, 20 mg daily; atorvastatin 40 mg/day; and Metformin 1000 mg twice/day. He checks his blood glucose once daily and reports fasting glucose values of 160-220 mg/dL (8.9–12.2 mmol/L). He has a sedentary desk job but is active, walking his dog 60 minutes daily without chest discomfort. He skis and hikes on weekends. He has no family history of heart disease

Exam: BP: 128/72. Pulse: 68. BMI 34. He is well virilized, and tests are 20 cc bilaterally. Findings on cardiopulmonary, abdominal, and neurologic examinations are normal.

Lab: (8 AM while fasting): Total testosterone - 480 ng/dL (300-900).
Total cholesterol: 215 mg/dL (<200). HDL: 42 mg/dL (>60). LDL: 105 mg/dL (<100). Tg: 210 mg/dL (<150). HbA1c: 8.5% (4-5.6%) (69 mmol/mol). Which is the best next step in managing this patient's erectile dysfunction?

A. Addition of a second drug to treat dyslipidemia
B. Calculation of free testosterone
C. Cardiac stress echocardiography
D. Intensification of a glucose-lowering regimen
E. Trial of an oral phosphodiesterase inhibitor

14.2. ANSWER: E) Trial of an oral 14-phosphodiesterase inhibitor

Most experts recommend testing for hypogonadism in men who have erectile dysfunction. Eugonadism is necessary for normal male sexual function, including normal tumescence, but serum total testosterone concentrations must be very low (<150 ng/dL [<5.2 nmol/L]) to cause erectile dysfunction. In this man with normal libido and a midrange, normal total testosterone concentration, hypogonadism is very unlikely to be the cause Thus, measurement of calculated free testosterone (Answer B) is unlikely to be useful in determining the etiology of his erectile dysfunction, even though many men with type 2 diabetes have low free testosterone and biochemical hypogonadism. Given that his total testosterone value is well within the normal range, his free testosterone is very unlikely to be below the normal range despite his obesity.

14.3. ANSWER: E) Trial of an oral 14-phosphodiesterase inhibitor

Optimizing glycemic control (Answer D) and lipid control (Answer A) might provide microvascular benefits, and only his lipids are currently reasonably controlled. While there is evidence that optimal glycemic control can reduce the risk of erectile dysfunction in men with diabetes, there is no evidence that reversal of established erectile dysfunction occurs with improved glycemic control. Once the diagnosis of erectile dysfunction is established, first-line therapy for men with and without diabetes is phosphodiesterase inhibitors (Answer E). Erectile dysfunction is a strong marker of cardiovascular disease. Sexual intercourse is typically about 3 to 4 metabolic equivalents. Walking a mile in 20 minutes is about 4 metabolic equivalents. Thus, while this patient has cardiovascular risk factors, he is not taking nitrates and engages in an active lifestyle without symptoms. Thus, cardiac stress echocardiography (Answer C) is incorrect.

Educational Objective: Recommend optimal treatment for a man with diabetes and erectile dysfunction.

15.1. A 34-year-old ♂ is being considered for testosterone therapy. He has been regularly strength training at his local gym for five years. Over the past year, he has noticed a plateau in his muscle development and weight gains compared to his peers. He also reports mild breast tenderness. He has normal sexual function and morning erections but has experienced a slight decrease in libido, which he attributes to changes in his body image. He has a normal reproductive history. He eats a high-protein, mostly plant-based diet. He has been married to his wife for ten years and has two children, ages nine and seven. He does not take any medications.

Exam: BP: 150/90. Pulse: 80. BMI: 26. He is muscular with 1 cm bilateral gynecomastia and normal male-pattern hair on his face and chest. He has mild acne on his chest. His testes are 20 cc bilaterally with no masses, and his phallus is normal.

Lab: Hematocrit 50% (41-51%). Total testosterone 600 ng/dL (300-900). Calculated free testosterone 26 ng/dL (9-30). LH 0.1 mIU/mL (1-9). Prolactin 5 ng/mL (4-23). TSH: 0.9 mIU/L (0.5-5). Ferritin: normal. Total cholesterol: 220 mg/dL (<200). LDL: 180 mg/dL (<100). HDL: 50 mg/dL (>60). Tg: 135 mg/dL (<150). Which is the most likely explanation for these findings?

A. Erythropoietin ("epo") use
B. Oral androstenedione use
C. Oral clomiphene use
D. Pituitary microadenoma
E. Subcutaneous hCG use

15.2. ANSWER: E) Subcutaneous hCG use. This patient exhibits signs of androgen excess (acne, gynecomastia, erythrocytosis) and is part of a gym culture where there is a high prevalence of anabolic steroid use. The marked LH suppression despite normal testosterone levels is a key feature of exogenous androgen use. Exogenous hCG (Answer E) mimics LH, causing increases in testosterone production and suppression of LH without testicular shrinkage that may occur with exogenous testosterone. A pituitary microadenoma (Answer D) suppressing LH to this degree would not support normal testosterone production. Erythropoietin (Answer A) increases hematocrit, but it would not suppress LH or cause stigmata of androgen excess. Androstenedione (Answer B) can be taken orally and is a weak androgen that some athletes abuse. Androstenedione is a precursor for testosterone.

15.3. ANSWER: E) Subcutaneous hCG use.
In large quantities, it may raise serum testosterone. However, oral androgens profoundly lower HDL cholesterol and, at high enough dosages to produce complete suppression of LH, would result in testicular shrinkage. Clomiphene citrate and enclomiphene (Answer C) are estrogen receptor modulators that can raise serum testosterone; however, due to a lack of estrogen-mediated negative feedback at the pituitary gland, they do not suppress LH

Educational Objective: Identify the clinical and laboratory findings that reflect abuse of performance-enhancing anabolic agents.

16.1. A 26-year-old transgender man seeks gender-affirming hormone therapy (testosterone). The patient meets the criteria for gender-affirming hormone therapy, and findings from baseline evaluation, including complete blood cell count and Papanicolaou test, are normal. His only medication is metformin, 1000 mg daily, for prediabetes.

Exam: BMI 30. findings are otherwise unremarkable.

During the visit, treatment options, expected results, potential risks, plans for future fertility, and the importance of regular monitoring are reviewed. Hormone therapy is initiated with testosterone enanthate injections, 200 mg every 2 weeks.

Which describes the best screening and monitoring during the first year of treatment?

A. Measure bone density at 1 year
B. Measure hemoglobin A1c every 6 months
C. Measure hematocrit or hemoglobin every 3 months
D. Measure serum total testosterone immediately before his testosterone enanthate injection every 3 months
E. Perform a Pap test at 1 year

16.2. ANSWER: C) Measure hematocrit or hemoglobin every 3 months

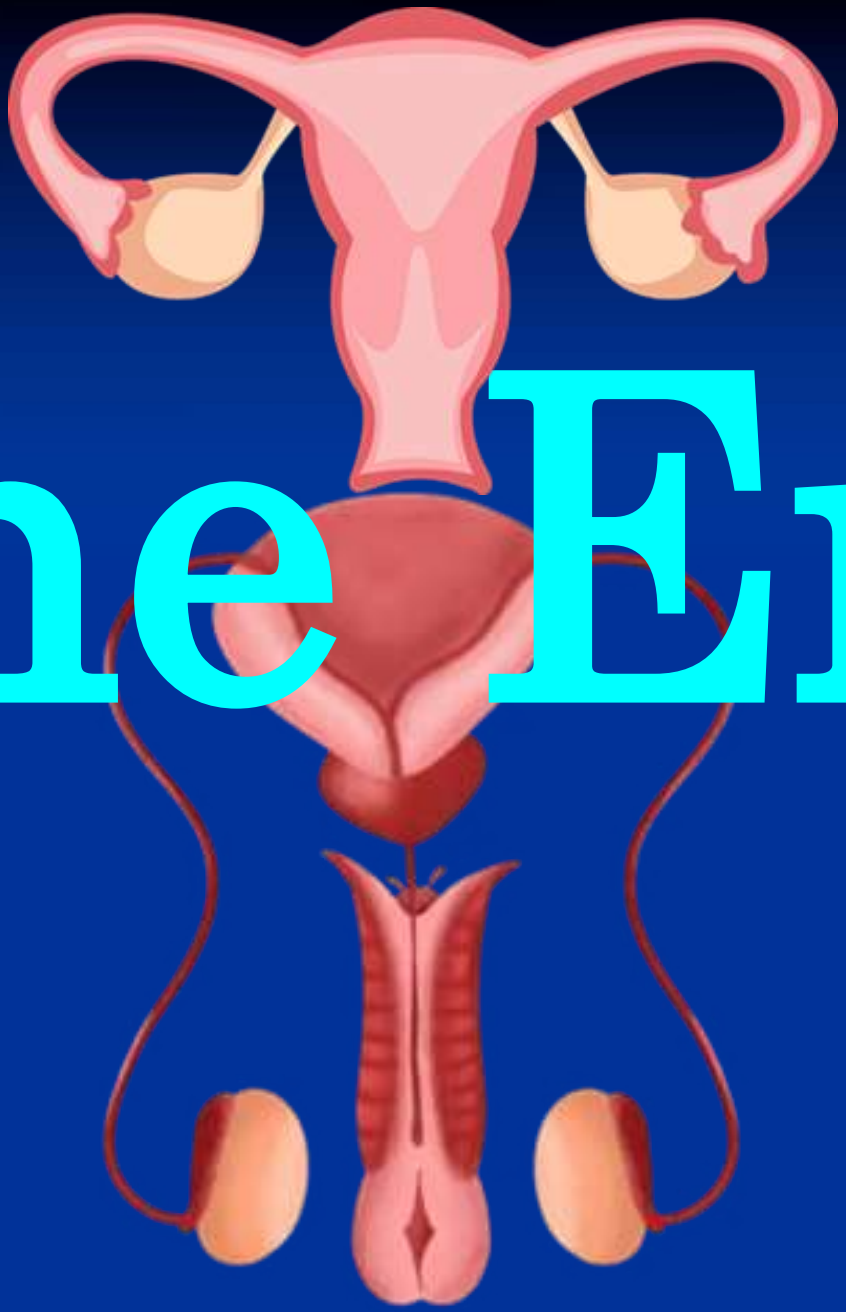
Testosterone administration at pharmacologic levels in women (or men) causes increased hematocrit and risk of polycythemia. This is a greater concern with parenteral testosterone administration, but it can be seen with testosterone gel as well. Therefore, the current Endocrine Society guideline suggests that hematocrit or hemoglobin be measured at baseline and every 3 months (Answer C) for the first year and once or twice yearly thereafter. Serum testosterone measurement (Answer D) is also essential, but this should ideally be assessed midway between injections or at least 2 hours after application of a transdermal preparation. HbA1c measurement (Answer B) is not a component of routine monitoring of hormone therapy for transgender men, and testosterone therapy has not been demonstrated to accelerate or increase the progression to diabetes in this population.

16.3. ANSWER: C)

Papanicolaou tests (Answer E) are performed if cervical tissue is present (many patients undergo hysterectomy and thus do not have cervical tissue). The schedule for cervical screening is the same as it is for transgender women (every 3 years).

Bone density monitoring at 1 year (Answer A) is not essential, as bone mineral density is expected to be maintained on testosterone therapy. Testosterone is converted peripherally to estradiol, and estradiol maintains bone.

Educational Objective: Identify the most important components of monitoring transgender men taking gender-affirming hormone therapy.



The End

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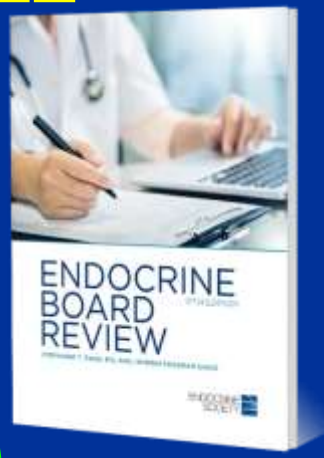
مراجعات البورد في الغدد

EBR.17

Bone and Calcium

Ca/Bone



الدكتور محمد الشعباني

1.1. A 75-year-old ♀ is referred for evaluation and treatment of osteoporosis. A recent DXA scan showed an L1-L4 T-score of -3.9, a left femoral neck T-score of -3.4, and a left one-third radius T-score of -5.9. She had been physically active and generally felt well until about seven months ago, when she developed progressively severe muscle weakness, fatigue, difficulty walking, and musculoskeletal pain. Five months ago, a whole-body nuclear bone scan showed increased uptake at the right femoral head, thought to be an insufficiency fracture. One month later, she had a stress fracture of the right foot (fifth metatarsal). For the past five years, her medications have included abacavir, raltegravir, and tenofovir for HIV treatment. She enters the examination room using a four-wheeled walker. She has a wide-based, waddling gait and difficulty rising from the chair.

Lab: Serum Ca: 8.8 mg/dL (8.2-10.2). Albumin 3.9 g/dL (3.5-5). Phosphate 2.2 mg/dL (2.3-4.7). 25OHD: 24 ng/mL (30-80). Total ALP: 182 U/L (50-120 U/L).

PTH: 58 pg/dL (10-65). AST: normal. GGT: normal. Cr: 1.4 mg/dL (0.6-1.1).

FGF23: < 50 RU/mL (<180). Which of the following best explains this patient's symptoms and abnormal laboratory findings?

A. Fanconi syndrome
B. Normocalcemic primary hyperparathyroidism
C. Osteoporosis
D. Tumor-induced osteomalacia
E. X-linked hypophosphatemia

1.2. ANSWER: A) Fanconi syndrome

Although this patient meets the World Health Organization criteria for a diagnosis of osteoporosis (Answer C), and it is likely that she does have osteoporosis, this does not explain her low phosphate and musculoskeletal symptoms. Tenofovir is known to cause Fanconi syndrome (Answer A) with renal phosphate wasting and osteomalacia. When patients with unrecognized osteomalacia, including osteomalacia caused by Fanconi syndrome, have been treated for osteoporosis with bisphosphonates, there have been serious adverse consequences, including a reduction in already low serum phosphate levels, worsening of musculoskeletal symptoms, and fractures. Every patient with apparent osteoporosis should be evaluated for factors contributing to low bone density and skeletal fragility with laboratory tests that include serum phosphate measurement. If low phosphate is found, the cause should be identified and corrected before starting osteoporosis medication. This patient had renal phosphate wasting due to tenofovir-induced Fanconi syndrome.

1.3. ANSWER: A) Fanconi syndrome

She was treated with oral phosphate and calcitriol, with discontinuation of tenofovir. Osteoporosis treatment was started only after serum phosphorus and alkaline phosphate returned to normal. Her PTH concentration is normal, so she does not have normocalcemic primary hyperparathyroidism (Answer B). X-linked hypophosphatemia (Answer E) may be first recognized in adults and is associated with low phosphate levels, but it is caused by high FGF-23, which she does not have. Tumor-induced osteomalacia (Answer D) should always be considered with adult-onset hypophosphatemia. However, her FGF-23. The concentration is low, and it would be expected to be high in the setting of tumor-induced osteomalacia.

Educational Objective:

Recognize osteomalacia caused by drug-induced Fanconi syndrome with hypophosphatemia.

REFERENCE(S)

2.1. A healthy and active 65-year-old ♀ is found to have osteoporosis on her first screening DXA, with a right femoral neck T-score of -2.8. Evaluation for contributing factors is unremarkable (comprehensive metabolic panel [including creatinine, calcium, albumin, and alkaline phosphatase measurement and liver function tests] and TSH and serum 1,25(OH)2D measurement). Alendronate, 70 mg weekly, is initiated. When she has a follow-up DXA 2 years later at the same facility, the report indicates that she has had a significant decrease in bone mineral density. The facility is accredited by the International Society for Clinical Densitometry, and her endocrinologist is confident that the comparison is valid.
Lab: PTH: 66 pg/mL (10-65). 25OHD: 22 ng/mL (30-80. Hemoglobin 11.6 g/dL (12.1-15.1). (with hypochromic microcytic indices). Urinary Ca: 48 mg/24 h (100-300).
Based on the lab findings, which is the most likely explanation for her suboptimal response to treatment with alendronate?

A. Celiac disease
B. Myeloma
C. Normocalcemic primary hyperparathyroidism
D. Poor adherence to therapy
E. Vitamin D deficiency

2.2. ANSWER: A) Celiac disease

Celiac disease (Answer A) is a recognized cause of osteoporosis, primarily due to calcium malabsorption resulting in hypocalciuria, and it may also cause iron deficiency anemia due to iron malabsorption. Measuring serum endomysial antibodies would be helpful, as they are almost always elevated with untreated celiac disease. The diagnosis of celiac disease can be confirmed with a small-bowel biopsy. Good adherence to a gluten-free diet is often followed by improvement in bone mineral density, as much or more than might be expected with medications, such as alendronate. Adherence to osteoporosis therapy is often poor (Answer D), but this does not explain this patient's anemia and hypocalciuria. Myeloma (Answer B) can cause anemia but not hypocalciuria. Hypocalciuria may be associated with secondary hyperparathyroidism and rules o t a diagnosis of normocalcemic primary hyperparathyroidism (Answer C). This patient's 25-hydroxyvitamin D level (Answer E) is lower than recommended according to some guidelines and sufficient according to others, but it is not low enough to cause decreasing bone density on alendronate.

Educational Objective:

Identify celiac disease as a potential cause of osteoporosis, even in the absence of gastrointestinal symptoms.

3.1. A 63-year-old ♀ is referred by her orthopedist for multiple poorly healing fractures. Her only prior treatment for osteoporosis was alendronate, which she took from age 49-54. Previous fractures include recurrent metatarsal stress fractures beginning at age 42, a left femoral shaft fracture from a fall at age 47, a right femoral shaft fracture from a fall at age 59, and a left midtibia fracture from a fall at age 62. She has a childhood history of recurrent respiratory failure, chronic bone pain, and difficulty keeping up with her peers in gym class
Exam: she has a slow, unstable gait using a wheeled walker, valgus (knock-kneed) deformity, and difficulty getting on the exam table.
DXA shows a left one-third radius T-score of -4.2, with the lumbar spine and hip invalid due to structural abnormalities and surgical hardware.
Lab: documents normal results of serum albumin-correct Ca, phosphorus, PTH, Cr, 25OHD, and 24-hour urinary Ca measurement. Results of serum protein electrophoresis are also normal.
Which of the following tests is most likely to lead to the correct diagnosis?

A. Genetic testing for pathogenic variants in the PHEX gene
B. Serum alkaline phosphatase measurement
C. Serum C-telopeptide measurement
D. Serum FGF-23 measurement
E. Urine maximum tubular reabsorption of phosphate/GFR (TmP/GFR)

3.2. ANSWER: B) Serum alkaline phosphate measurement

This patient has many symptoms and signs of childhood-onset hypophosphatemia (recurrent metatarsal stress fractures, chronic bone pain, childhood respiratory failure, recurrent poorly healing fractures). If the serum alkaline phosphate concentration (Answer B) is below the age-adjusted reference range, she would meet standard criteria for a diagnosis of hypophosphatemia and may be a candidate for treatment with asphotase alfa. Measurement of FGF-23 (Answer D) is most useful to determine whether hypophosphatemia due to renal phosphate wasting is FGF-23-mediated. Since this patient does not have hypophosphatemia, measuring FGF-23 is unlikely to be helpful. Measurement of serum C-telopeptide (Answer C), a marker of bone resorption, can help evaluate the rate of bone remodeling, but it is not going to uncover this patient's diagnosis

She does not have hypophosphatemia, and the rate of renal tubular reabsorption of phosphate (Answer E) does not need to be evaluated Genetic testing for pathogenic variants in the PHEX gene (Answer A), responsible for X-linked hypophosphatemia, is not necessary since she has normal serum phosphate.

Educational Objective:

Identify adults with hypophosphatasia.

4.1. An 83-year-old ♂ is seen for management of severe osteoporosis. Recent MRI shows subacute vertebral fractures at T12 and L1. DXA left total hip T-score is -2.8. He has a history of partial gastrectomy for peptic ulcer disease with gastrointestinal bleeding. He is seen by a rheumatologist for rheumatoid arthritis and an oncologist for monoclonal gammopathy of undetermined significance and chronic iron deficiency anemia. Medications include prednisone (currently 5 mg daily), hydroxychloroquine, pantoprazole, and episodic infusions of carboxymaltose. Lab: Albumin-adjusted serum Ca: normal. Phosphorus: normal. ALP: normal. Cr: normal. 25OHD: normal. PTH: 83 pg/mL (10-65). Anabolic therapy is recommended, but he declines and instead chooses treatment with Denosumab. Three weeks after his first dose of Denosumab, he describes feeling weak and dizzy. His family takes him to the hospital, where he is found to have supraventricular tachycardia.
Lab: Albumin-corrected serum calcium 6.1 mg/dL (8.2-10.2 mg/dL).
Phosphate 1 mg/dL (2.3-4.7). His heart rhythm disturbance is corrected, and he is given intravenous calcium and phosphate. He is discharged 3 days later, but hypocalcemia and hypophosphatemia persist for months, requiring repeated infusions and high-dose oral supplements Which of the following is the most likely cause of this patient's prolonged hypocalcemia and hypophosphatemia?

A. Denosumab
B. Denosumab + ferric carboxymaltose
C. Ferric carboxymaltose
D. Malabsorption due to partial gastrectomy
E. Pantoprazole

4.2. ANSWER: B) Denosumab + ferric carbomymaltose

There have been reports of denosumab (Answer A) causing hypocalcemia and hypophosphatemia and reports of ferric carboxymaltose (Answer C) and some other iron infusions causing hypophosphatemia, but the combination of denosumab and carboxymaltose (Answer B) has been reported to be especially troublesome.

Denosumab can lower serum calcium due to its robust antiremodeling effect on bone, with the resulting compensatory increase in PTH probably contributing to lowering the phosphate level. Ferric carboxymaltose increases FGF-23, causing reduced renal tubular reabsorption of phosphate. This patient—unknown to the physician prescribing denosumab—received an infusion of ferric carboxymaltose about 5 days earlier

He may have some malabsorption due to his partial gastrectomy (Answer D), but this is unlikely to be the cause of his prolonged hypocalcemia and hypophosphatemia since his baseline values were normal.

Pantoprazole (Answer E) is known to cause hypomagnesemia in some patients, but not the metabolic abnormalities seen here.

Educational Objective:

Describe the synergistic effects of denosumab and ferric carboxymaltose on calcium and phosphate metabolism.

5.1. A 51-year-old ♂ has had chronic back pain since involvement in a major motor vehicle accident at the age of 39. He was treated with physical therapy and a variety of anti-inflammatory agents. He was ultimately prescribed opioids, to which he became addicted. Dilaudid used to manage his addiction, but after his physician moved out of the community, Dilaudid was abruptly stopped with no arrangements for follow-up. He struggled to overcome withdrawal but was able to stay off opioids. However, he subsequently developed progressively severe generalized bone pain, especially from the knees down, as well as numbness in both lower legs and problems with poor balance. He was seen in local clinics where metastatic bone cancer was suspected but never confirmed. He now presents for an office visit for evaluation and relief of symptoms. Exam: his hands and feet appear enlarged. Albumin-corrected serum Ca: normal. Mg: normal. Phosphate 1.8 mg/dL (2.3-4.7). PTH: 422 pg/mL (10-65). ALP: 677 U/L (50-120). 25OHD: 10 ng/mL (30-80). Fasting serum C-telopeptide 5.4 ng/mL (0.5–2 ng/mL). X-ray survey shows generalized skeletal sclerosis. Bone marrow biopsy reports hypocellularity, increased reticulin fibrosis, and increased osteoblastic and osteoclastic activity, suggestive of Paget's disease. Which of the following most likely explains his symptoms and findings?

A. LRPS high bone mass pathogenic variant with late onset of symptoms
B. Normocalcemic primary hyperparathyroidism
C. Secondary hyperparathyroidism
D. Severe osteomalacia
E. Skeletal fluorosis

5.2. ANSWER: E) Skeletal fluorosis

Skeletal fluorosis (E) is confirmed by the finding of greatly elevated serum fluoride. When confronted with this information, he admits to "huffing" Dust-Off (compressed gas containing difluoroethane) for many years, sometimes as much as 12 cans per day, to deal with his chronic pain and opioid addiction. This is now a well-recognized cause of high bone mass due to the direct anabolic effects of fluoride on the skeleton. DXA shows very high bone density, with a left total hip T-score of 5.6. There is no effective treatment for skeletal fluorosis; it can take many years after removing the source of fluoride (huffing, in this case) for fluoride levels to normalize and symptoms to resolve. Although vitamin D deficiency can cause osteomalacia (Answer D) and secondary hyperparathyroidism (Answer C), these conditions would not explain skeletal sclerosis. Normocalcemic primary hyperparathyroidism (Answer B) is excluded because of his very low vitamin D level An LRPR pathogenic variant (Answer A) can cause high bone mass, but it would not explain late-onset disease and the constellation of laboratory findings.

Educational Objective:

Identify findings of skeletal sclerosis.

6.1. A 66-year-old ♀ with class III obesity living in Arizona has developed two spontaneous skin ulcers on the anterior abdominal wall (each measuring 1 inch (2.5 cm) in diameter).
She has kidney failure due to hypertensive nephropathy and has been on hemodialysis for the past five years. She has secondary hyperthyroidism with very high PTH levels and high serum phosphorus, treated with calcitriol and sevelamer carbonate. Chest x-ray shows several punctate pulmonary nodules in the right lower lung. She scratched her skin lesion, which subsequently became slightly purulent and then developed areas of eschar.
Lab: WBC: 21,000/µL (4500-11,000). Ca: 8.6 mg/dL (8.2-10.2). Albumin 3.3 g/dL (3.5-5). Phosphate: 8.3 mg/dL (2.3-4.7 mg/dL). PTH: 720 pg/mL (10-65).
Her condition does not respond to treatment with empiric antibiotics and antifungal agents for possible coccidiomycosis, which is endemic in Arizona. Abdominal CT shows anterior abdominal wall subcutaneous calcification. Skin biopsy shows possible thrombus in the upper dermis and calcified deposits in the subdermis. She then undergoes 3.5-gland parathyroidectomy, more intensive hemodialysis, and hyperbaric oxygen, with eventual resolution of her skin lesions over the next 6 months Which of the following is the most likely diagnosis that explains this patient's skin lesions?

A. Antiphospholipid antibody syndrome
B. Calciphylaxis (calcific uremic arteriolopathy)
C. Hypertensive ischemic/Martorell ulcers
D. Panniculitis ossificans
E. Pyoderma gangrenosum

6.2. Answer B) Calciphylaxis. (Calciphylaxis (answer B) is the most likely diagnosis. This very rare disease has a high mortality rate (up to 80%) and is associated with risk factors such as chronic kidney disease, obesity, and high PTH. The pathogenesis is unclear, although it is characterized by microvascular calcification and thrombus formation and typically involves imbalances of calcium and phosphate metabolism. There are no consensus guidelines for the diagnosis and management of this disorder, although treatments aimed at inhibiting calcification, such as sodium thiosulfate and bisphosphonates, have been reported to be beneficial. Antiphospholipid antibody syndrome (Answer A), panniculitis ossificans (Answer D), hypertensive ischemic/Martorell ulcers (Answer C), and pyoderma gangrenosum (Answer E) are causes of skin ulcers, but they are less likely to explain this patient's findings. Antiphospholipid syndrome is a hypercoagulable disorder with arterial and venous blood clots, with risk factors that include autoimmune diseases, malignancy, and infections. Panniculitis ossificans (also called heterotopic ossification) is characterized by progressive formation of lamellar bone outside the skeleton, often involving fat necrosis and histopathological findings of hemosiderin-laden Macrophages. Hypertensive ischemic/Martorell ulcers are typically associated with extreme ischemic pain in patients with severe hypertension. Pyoderma gangrenosum is characterized by relapsing inflammatory ulcers with poorly defined, erythematous, violaceous raised borders, possibly due to neutrophilic dermatosis without infections.

Educational Objective:

Identify patients with calciphylaxis (calcific uremic arteriolopathy).

7.1. A 24-year-old ♂ who is a long-distance runner has been experiencing progressive pain and swelling in the anterior right lower leg over the past 18 months. His primary care physician orders x-rays that show a lytic lesion in the mid-tibia with a ground-glass appearance, thinning of the cortex, and endosteal scalloping, consistent with fibrous dysplasia. The primary care provider reviews what is known about fibrous dysplasia and discovers this is associated with extraskeletal manifestations of McCune-Albright syndrome. The patient is referred for further evaluation and treatment

Exam: he has erythema, swelling, and tenderness over the middle third of the anterior tibia. There are no café-au-lait lesions. A thorough endocrine evaluation reveals that he has hypophosphatemia, renal phosphate wasting, and high FGF23 with elevated total ALP. He has a normal kidney profile and normal measurements of bicarbonate, albumin-corrected serum Ca, and 25OHD. Whole-body imaging using bone scintigraphy shows no abnormalities other than at the right tibia. Monostotic fibrous dysplasia with FGF-23-mediated hypophosphatemia is diagnosed. The main concern is that the progressively severe pain is adversely affecting his quality of life and that he may be at risk for fracture.

Which of the following is the most appropriate initial therapy for this patient?

A. Burosumab and romosozumab
B. Burosumab, then add subcutaneous calcitonin
C. Denosumab
D. Oral phosphate and calcitriol, then consider antiresorptive therapy
E. Zoledronic acid

7.2. ANSWER: D) Oral phosphate and calcitriol, then consider antiresorptive therapy

The best approach for this patient is to treat with oral phosphate and calcitriol to correct hypophosphatemia and osteomalacia and then consider antiresorptive therapy (Answer D), as this addresses normalization of serum phosphate and presumed osteomalacia (consistent with high total serum alkaline phosphatase) before starting antiresorptive therapy for bone pain. In addition, it would be prudent to modify his physical activities if the risk of fracture is considered high.

Elevated FGF-23 and resulting hypophosphatemia with fibrous dysplasia are related to the skeletal burden of disease and are not considered to be a criterion for diagnosing McCune-Albright syndrome. Treating his hypophosphatemia with burosumab and skeletal fragility with romosozumab (Answer A) is incorrect because burosumab is not FDA-approved for the treatment of hypophosphatemia in patients with fibrous dysplasia, and romosozumab is not FDA-approved for treatment in men, even though both agents may be effective under these circumstances.

Starting denosumab (Answer C) to reduce bone pain and starting zoledronic acid (Answer E) to reduce bone pain are incorrect because the phosphate level should be corrected first before starting these drugs. However, there is evidence that these medications can reduce bone pain from fibrous dysplasia.

Beginning treatment with burosumab until phosphate is normal and then adding subcutaneous calcitonin (Answer B) is incorrect because burosumab is not FDA-approved for this purpose and calcitonin is unlikely to be effective.

Educational Objective:

Explain the principles of pharmacological therapy for fibrous dysplasia in adults.

8.1. A 58-year-old ♀ with class III obesity underwent bariatric surgery (Roux-en-Y procedure) 6 years ago. She subsequently lost 31 kg and regained 5 kg. Since her procedure, she has had difficulties with postprandial loose stools and intermittent diarrhea. She is sedentary due to chronic fatigue and generalized musculoskeletal pain. She took nutritional supplements for the first several years after surgery, but has not taken them regularly in recent years. She has not had consistent medical care because she lost her health insurance. Six months ago, she experienced an insufficiency fracture of the pelvis, triggering bone density testing that showed a lowest relevant T-score of -2.7 at the left femoral neck. A comprehensive metabolic panel shows normal kidney and liver function.

Lab: Serum Ca: 8.1 mg/dL (8.2-10.2). Albumin: 3.6 g/dL (3.5-5). Total ALP: 135 U/L (50-120)

She is treated for severe osteoporosis with IV Zoledronic acid, 5 mg administered over 15 minutes. The following day, she develops severe pain in her hips and knees, headache, fever, nausea, and muscle cramps. She goes to an urgent care center for evaluation. She is found to be hypocalcemic and is treated with IV Ca infusions and sent home with instructions to take Ca + VD supplements. She is then referred to endocrinology for evaluation of hypocalcemia.

Which of the following is the most likely explanation for this patient's hypocalcemia?

A. Acute-phase reaction
B. Drug-induced renal tubular acidosis
C. Hypoparathyroidism
D. Vitamin D deficiency
E. Zoledronic acid infusion time was too fast

8.2. ANSWER: D) Vitamin D deficiency

Vitamin D deficiency (Answer D) is a common occurrence in patients who have undergone a Roux-en-Y procedure; these patients sometimes need very large dosages of vitamin D supplements to maintain blood levels in an acceptable range. Her elevated serum alkaline phosphatase concentration suggests that she may have had osteomalacia, which can be caused by severe vitamin D deficiency.

The patient received the zoledronic acid infusion over 15 minutes, which is consistent with standard recommendations (thus, Answer E is incorrect). However, there is evidence that longer infusion times may be associated with a lower risk of an acute-phase reaction and perhaps a lower risk of adverse effects on the kidneys.

There is nothing to suggest she has hypoparathyroidism (Answer C) since the baseline albumin-corrected calcium value is normal.

She has symptoms of an acute-phase reaction (Answer A), but this does not explain hypocalcemia. Zoledronic acid given over at least 15 minutes in patients with normal kidney function is not expected to cause renal tubular acidosis (Answer B).

Educational Objective:

Optimize safety with administration of zoledronic acid.

9.1. A 67-year-old ♀ with osteoporosis and previous wrist fracture, who has a fall and a previous wrist fracture from a fall at age 58, has been treated with denosumab, 60 mg SC every 6 months, for the past 2 years. She is generally healthy except for chronic back pain and mild fatigue. She cannot take oral bisphosphonates due to dysphagia. She has recently moved to the community, and this is her first appointment at this clinic. She is hoping to continue denosumab treatment.

Lab tests are ordered in anticipation of giving the next denosumab dose: Kidney function, normal. Albumin-corrected serum Ca: norma. 25OHD: normal. ALP: 42 U/L (50-120). Which is the best next step in this patient's management?

A. Combine denosumab with abaloparatide
B. Request previous laboratory studies
C. Stop denosumab
D. Switch treatment to teriparatide
E. Switch treatment to zoledronic acid

9.2. ANSWER: B) Request previous laboratory studies

Although it is possible that this patient has unrecognized adult-onset hypophosphatasia, it is highly unlikely that this rare disease is responsible for the low alkaline phosphatase value, which is commonly seen as an expected result of treatment with denosumab. Stopping denosumab (Answer C) would not be recommended, since it is likely that she has unrecognized adult-onset hypophosphatasia Requesting previous laboratory studies (Answer B) to establish baseline serum alkaline phosphatase before denosumab was started is the best approach because the most likely scenario is that the patient had a low-normal serum alkaline phosphatase concentration before starting denosumab, and the reduction in bone remodeling with this drug resulted in a level below the reference range. We know from the phase 2 trial with denosumab that a 60% decrease of bone-specific alkaline phosphatase occurs, meaning that a 30% decrease of total alkaline phosphatase might be seen. Documenting a low-normal total alkaline phosphatase value in this patient before starting denosumab would confirm the suspicion that she is having a normal therapeutic response. Switching from denosumab to teriparatide (Answer D) is incorrect, since this sequence of therapy has been associated with sustained bone density decreases at the hip in a clinical trial. Combining denosumab with abaloparatide (Answer A) is incorrect, as there are no data regarding the efficacy of this combination for reducing the risk of an atypical femur fracture. Switching from denosumab to zoledronic acid (Answer E), a milder antiresorptive agent, is incorrect since there is no evidence of oversuppression of bone remodeling, which lacks a consensus definition.

Educational Objective:

Explain the expected biomarker response to denosumab treatment.

10.1. 10. A 54-year-old postmenopausal ♀ presents a follow-up of postsurgical hypoparathyroidism. She underwent parathyroidectomy of 3.5 glands at age 49 to treat longstanding primary hyperparathyroidism secondary to parathyroid hyperplasia, with failed autotransplantation of a half-gland to her forearm. Her serum Ca has been successfully maintained in the low end of the normal range with Ca supplements and calcitriol.
The patient asks whether she should have bone density testing now
Which of the following is the most appropriate response to this patient's question?

Answer	Should she have bone density testing now?	Rationale
A	No	Wait until age 65 for bone density testing, which is the standard time for first screening according to current clinical practice guidelines.
B	No	Hypoparathyroidism is a low bone turnover state associated with normal or high bone density.
C	No	Hypoparathyroidism is known to be protective against postmenopausal bone loss for at least 10 years after surgery, so there is no need for bone density testing.
D	Yes	Recommended for spine, hip, and forearm
E	Yes	Recommended for forearm only

10.2. ANSWER: D) Yes, bone density spine, hip, and forearm

This patient should have bone density testing now (spine, hip, and forearm) (Answer D) because low bone density/osteoporosis is common in individuals with hyperparathyroidism. A recent report found that about one-third of patients with hypoparathyroidism have osteoporosis according to bone density criteria or prior fracture. This is not surprising, since most patients who have hypoparathyroidism are post-surgical, and patients with longstanding primary hyperparathyroidism before surgery are at risk for bone loss and fractures. Also, most current guidelines recommend bone density testing for postmenopausal women between ages 50 and 65 years when a risk factor, such as primary hyperparathyroidism, is present.

Waiting until age 65 to have a bone density test (Answer A) (standard time for the first screening bone density test according to current clinical practice guidelines) is incorrect because a delay in testing might represent a missed opportunity to intervene to reduce fracture risk

Holding off on bone density testing now because hypoparathyroidism is a low bone turnover state that is associated with normal or high bone density (Answer B) might represent the conventional wisdom about bone health and hypoparathyroidism, but it is incorrect because it does not reflect the current state of knowledge. Bone density testing for the forearm only (Answer E) is incorrect because she is at risk for osteoporosis that may be detected at skeletal sites in addition to the forearm. There is no evidence that hypoparathyroidism prevents osteoporosis or fractures over any length of time (Answer C).

Educational Objective:

Identify indications for skeletal health assessment in patients with hypoparathyroidism

11.1. A 62-year-old ♀ had a sacral fracture and multiple vertebral fractures in the midthoracic spine from a fall off the first step of a ladder. Bone density testing documented the lowest relevant T-score to be -5.2 at the lumbar spine (L1-L4). She has no risk factors for osteoporosis other than being postmenopausal, estrogen deficient, and being white. There is no family history of musculoskeletal disease. She had a normal childhood and early adulthood. She had breast cancer at age 56 years, treated with lumpectomy, radiation therapy, and an aromatase inhibitor for 5 years. Her coronary Ca score is 119.

Lab: Ca: normal. Phosphate: normal. PTH: normal. 25OHD: normal.

ALP: 41 U/L (50-120). Suspected hypophosphatasia is confirmed by documenting a high level of serum pyridoxal 5'-phosphate (vitamin B) and a pathogenic Heterozygous variant in the ALPL gene. A transiliac bone biopsy shows no evidence of osteomalacia. There is a clinical dilemma in starting treatment to reduce fracture risk because antiresorptive agents (e.g., bisphosphonates, denosumab) and hypophosphatasia may have additive effects in increasing the risk of atypical femoral fractures. Which statements is correct about this patient's management?

A. Asforase alfa is indicated because of high fracture risk
B. Bisphosphonates are contraindicated because of high risk of atypical femoral fracture
C. Pharmacological therapy for osteoporosis should be considered
D. Romosozumab has been shown to enhance fracture healing in patients with hypophosphatasia
E. Strontium ranelate is the treatment of choice

11.2. ANSWER: C) Pharmacological to be considered

Bisphosphonates are analogues of inorganic pyrophosphate, which is presumably already high in individuals with hypophosphatasia. Therefore, it is thought that their use in such patients might be harmful. However, in patients with a very high fracture risk due to osteoporosis and very mild or totally asymptomatic hypophosphatasia, the benefits of treatment with a bisphosphonate, or perhaps denosumab, might outweigh the risk of atypical femoral fracture. Therefore, pharmacological therapy for osteoporosis should be considered for this patient (Answer C). Asfotase alfa (Answer A) is an enzyme replacement therapy that is only indicated for perinatal/infantile and juvenile-onset disease. Although bisphosphonates should be used with great caution in patients with hypophosphatasia, if at all, they are not contraindicated (Answer B).

There is no evidence that romosozumab enhances fracture healing in patients with hypophosphatasia (Answer D). There is no evidence to suggest that strontium ranelate is the treatment of choice (Answer E) in this setting.

Educational Objective:

Identify treatment options for patients who have osteoporosis and hypophosphatasia

12.1. A 40-year-old ♀ is found to have a serum Ca level that is mildly but consistently elevated over several months of observation (ranging from 10.3–10.9 mg/dL [2.6–2.7 mmol/L]). Her PTH level ranges from 67-78 pg/mL (10–65) over multiple measurements, and her serum 25OHD is 33 ng/mL. A 24-hour urine collection reveals the calculated Ca/Cr-CL ratio to be 0.01. Her parents are deceased, and she has no siblings or children. No previous lab results are available. She feels well. Which of the following is the best next step in this patient's management?

A. Bone mineral densitometry (DXA) testing
B. Continued annual monitoring
C. Genetic testing for a pathogenic variant in the calcium-sensing receptor gene (CASR)
D. Referral to a surgeon for 4-gland parathyroid exploration
E. Sestamibi parathyroid scan

12.2. ANSWER: C) Genetic testing for a pathogenic variants in the Ca sensing receptor gene (CASR): Does this patient have familial hypocalciuric hypercalcemia (FHH) or primary hyperparathyroidism? Answering this question might be easier if she had documentation of previous serum calcium measurements (normal serum calcium values in the past would make FHH unlikely) or relatives in whom serum calcium measurements could be obtained. She is young (age <50 years), so surgery (Answer D) would be recommended if she has primary hyperparathyroidism. However, surgery should not be performed until her diagnosis is confirmed. Similarly, imaging with a sestamibi scan (Answer E) should not be done until FHH is ruled out. Bone mineral density testing (Answer A) would not be helpful with the differential diagnosis, although bone density much lower at the one-third radius compared with density at the lumbar spine and hip would be consistent with longstanding hyperparathyroidism. Continued annual monitoring (Answer B) would not provide any additional information.

12.3. ANSWER: C) Continued annual monitoring (Answer B) would not provide any additional information. The 24-hour urine calcium-to-creatinine clearance ratio is key to considering FHH and came back low at 0.01. The ratio is calculated as follows: [urine calcium (mg/24 h) x serum creatinine (mg/dL)] / [urine creatinine (mg/24 h) x serum calcium (mg/dL)]. The most common form of FHH, known as FHH type 1, is caused by inactivating pathogenic variants in the gene encoding the calcium-sensing receptor (CASR). Recently, pathogenic variants in the GNAII gene have been shown to cause FHH type 2. Additionally, variants affecting codon 15 in the APZS1 gene have been described as FHH type 3. The best next step in this patient's management is genetic testing for a pathogenic variant in CASR (Answer C). Individuals with FHH continue to secrete PTH because the inactivated calcium-sensing receptor is reading a low serum calcium level.

12.4. ANSWER: C) This also occurs in the renal tubular calcium-sensing receptor, where it leads to renal calcium conservation (decreased renal calcium excretion). The end result is hypercalcemia and hypocalciuria. A low ratio of calcium clearance to creatinine clearance (<0.01) is consistent with FHH and should be followed by confirmatory genetic testing. If the patient has FHH, one of her parents most likely had the same pathogenic variant, as transmission is autosomal dominant (although this cannot be confirmed because her parents are deceased). Several different variants have been described, and a negative result for any of the known variants would not conclusively rule out FHH. Because primary hyperparathyroidism is much more common than FHH, should the diagnosis still be unclear after CASR genetic testing, parathyroid surgery should be strongly considered in view of her young age.

Educational Objective:

Distinguish familial hypocalciuric hypercalcemia from primary hyperparathyroidism

13.1. A 65-year-old ♀ was found to have high PTH 87 pg/mL as part of an evaluation for osteopenia documented on routine DXA testing (lowest T-scores: -2.1 in the lumbar spine and -1.6 in the left femoral neck). Her serum Ca range 9.8-10.2 mg/dL (2.5–2.6 mmol/L), within the lab reference range, and ionized Ca: normal. 25OHD: 48 ng/mL. She has been taking 2000 IU (50 mcg) of VD/day for several years. Her dietary Ca intake 600 mg/day, and she has been taking supplemental Ca 600 mg/day, for about 1 year.

Additional lab test results:

Urinary Cr 0.9 g/24 h (1-2 g/24 h). Urinary Ca: 180 mg/24 h (100-300). Phosphate 2.6 mg/dL (2.3-4.7). Albumin 4.3 g/dL (3.5-5). She has no history of kidney stones, fractures, or loss of height and no relevant family history. A repeated PTH: 79 pg/mL. Which is the most appropriate next step?

A. Double Ca supplementation + measure S.Ca + PTH again in 3 months
B. Measure serum Ca and PTH every 3 months
C. Order DXA of the one-third distal radius
D. Order kidney US
E. Order sestamibi parathyroid scan

13.2. ANSWER: C) Order DXA of the one-third distal radius

This patient most likely has normocalcemic primary hyperparathyroidism, which is defined as persistently normal total and ionized serum calcium levels in the setting of persistently elevated serum intact PTH, along with normal levels of 25-hydroxyvitamin D, serum creatinine, and 24-hour urinary calcium excretion. Such patients are often discovered during a workup for low bone mineral density. It is important to obtain DXA of the one-third distal radius (Answer C) because this site, rich in cortical bone, is most susceptible to the bone-resorbing effects of sustained hyperparathyroidism. If she has osteoporosis at this site, she would meet criteria for parathyroid imaging and surgery. Longitudinal studies indicate that parathyroidectomy improves bone mineral density in patients with both hypercalcemic and normocalcemic primary hyperparathyroidism For patients who decline surgery or are not surgical candidates, alendronate has been shown to significantly improve bone mineral density. Cinacalcet, which is US FDA approved for the treatment of primary hyperparathyroidism in nonsurgical patients, has not been shown to improve bone mineral density

13.3. ANSWER: C) Order DXA of the one-third distal radius

Sestamibi parathyroid scans (Answer E) detect only approximately 80% of abnormal parathyroid tissue, and there can be false-negative results. Sestamibi would not be indicated unless parathyroid surgery was planned. Without a personal or family history of kidney stones or an abnormally high urinary calcium excretion, imaging for kidney stones (Answer D) would not be the most appropriate next step in a woman of this age She is already getting enough calcium, so doubling calcium supplementation (Answer A) is unlikely to affect her serum PTH level. Many patients with normocalcemic hyperparathyroidism eventually demonstrate elevated serum calcium levels, but measuring calcium and PTH every 3 months (Answer B) is excessive. Most clinicians recommend retesting serum calcium and albumin every 6 to 12 months. The recommendations for the evaluation of patients with asymptomatic primary hyperparathyroidism are outlined (see box).

Educational Objective

Evaluate normocalcemic hyperparathyroidism

13.4. ANSWER: C) Order DXA of the one-third distal radius

A summary of panel recommendations for evaluation
Biochemical 1. Measure adjusted total serum calcium (ionized if NPHPT is consideration), phosphorus, intact PTH, 250 HDL, creatinine
Skeletal 2. Three-site DXA (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (VFA or vertebral X-rays). As an adjunctive test, the TBS can be helpful if available.
Renal 3. eGFR or, preferably, creatinine clearance, full 24-hour urinary calcium. Imaging for nephrolithiasis/nephrocalcinosis. In those with hypercalciuria, a stone risk profile is recommended. In those with stones (an indication for surgery), a stone risk profile is recommended whether or not the patient has hypercalciuria.

14.1. A 53-year-old ♀ presents with a new diagnosis of osteopenia. She had a hysterectomy three years ago for fibroids and developed hot flashes and night sweats last year. The hot flashes interfere with her work during the day and her sleep at night. Last month she fell and broke her wrist. A DXA performed at that time revealed T-scores of -2.4 at the lumbar spine and -2.3 at the femoral neck. She is otherwise very healthy, up-to-date on all health care screenings, and does not smoke cigarettes. BMI: 22 kg/m^2. Findings from a metabolic workup for secondary causes are negative.

Which of the following is the best recommendation for this patient?

A. Calcitonin
B. Estradiol patch
C. Paroxetine
D. Raloxifene
E. Risedronate

14.2. Answer: B) Estradiol patch

Estrogen therapy (Answer B) remains the most potent therapy for postmenopausal vasomotor symptoms and has also been shown to stop bone loss and reduce osteoporotic fractures in large clinical trials. For a healthy woman relatively early in menopause with both menopausal symptoms and osteopenia, estrogen therapy is an excellent option. Given that she had a hysterectomy, no progestin is needed, but even if she had an intact uterus, the choice of combination estrogen and progesterone would be a good therapy for her.

Paroxetine (Answer C) is US FDA approved for the treatment of moderate to severe menopausal vasomotor symptoms, but it would not improve bone health.

Raloxifene (Answer D) would be useful for bone health, but it could actually worsen her hot flashes. Risedronate (Answer E) is a potent antiosteoporosis agent, but it would not improve her vasomotor symptoms

Calcitonin (Answer A) has limited effectiveness for osteoporosis and would not help menopausal symptoms.

Educational Objective

Recommend estrogen therapy as an approved option for treating menopausal symptoms and preventing osteoporosis

15.1. A 78-year-old man is found to have a ALP: 185 U/L (3.09 µkat/L). Nuclear medicine bone scan shows increased activity in the right iliac wing. Radiographs of the area are consistent with Paget's disease. He has no symptoms.
Which treatments should be recommended?

A. Alendronate
B. Calcitonin
C. Denosumab
D. No treatment
E. Zoledronic acid

15.2. ANSWER: D) No treatment.

Most patients with Paget's disease are asymptomatic and do not require treatment (thus, Answer D is correct). When treatment is necessary, the best pharmacologic agent for Paget's disease appears to be zoledronic acid (Answer E). Head-to-head clinical trials have shown that risedronate is better than alendronate (Answer A) and zoledronic acid is better than risedronate. Calcitonin (Answer B) is considered the weakest agent and is rarely used for Paget's disease.

Denosumab (Answer C) is not approved for the treatment of Paget's disease.

Indications for treatment in an asymptomatic patient include the following:

Involvement of a weight-bearing bone (e.g., spine or leg)

Involvement near a joint

Involvement of the skull

Serum alkaline phosphatase level greater than 3 times the upper normal limit

Educational Objective

Determine when it is necessary to treat Paget's disease.

16.1. A 56-year-old woman with end-stage 16 kidney disease due to hypertension has been on hemodialysis for 8 years. She is referred due to a pelvic fracture with a femoral neck T-score of -2.2. Medications for the past 6 years include calcitriol, 0.5 mcg twice daily, and cinacalcet, 90 mg twice daily Lab results: Serum Ca: 8.1 mg/dL (8.2-10.2). Phosphate 5.2 mg/dL (2.3-4.7). 25OHD: 24 ng/mL (30-80). PTH: 120 pg/mL (10-65). ALP: 48 U/L (50-120). An iliac crest biopsy is performed after double-tetracycline labeling. Which is most likely to be found on this patient's bone biopsy?

A. Adynamic bone disease
B. Mixed renal osteodystrophy
C. Osteomalacia
D. Osteoporosis
E. Osteitis fibrosa cystica

16.2. ANSWER: A) Adynamic bone disease. The bone biopsy in this patient is most likely to show adynamic bone disease (Answer A), a variety of chronic kidney disease-mineral bone disorder (previously referred to as renal osteodystrophy). Adynamic bone disease is characterized by reduced osteoblasts and osteoclasts, markedly low bone turnover, and no osteoid accumulation. It occurs in a high percentage of patients on dialysis (either peritoneal or hemodialysis) but also in patients with chronic kidney disease on conservative treatment. Serum PTH levels in patients with adynamic bone disease are relatively low; however, serum PTH levels in patients with chronic kidney disease without adynamic bone disease are generally higher than normal, so the PTH level in this patient is much lower than expected. In patients with end-stage kidney disease, there is resistance to PTH, due at least in part to increased N-terminal truncated PTH (7-84), which counteracts the effect of the 1-84 whole molecule on bone.

16.3. ANSWER: A) Adynamic bone disease. This can be exacerbated by the use of cinacalcet, as well as overly aggressive treatment with calcitriol, both of which reduce PTH secretion. The low alkaline phosphatase is consistent with a low bone turnover state. Osteomalacia (Answer C) would be characterized by a much lower 25-hydroxyvitamin D level and a higher alkaline phosphatase level. Osteitis fibrosa cystica (Answer E) would be associated with very high PTH levels and secondary or tertiary hyperparathyroidism. Mixed renal osteodystrophy (Answer B) would be associated with elements of both hyperparathyroidism and osteomalacia. Osteoporosis (Answer D) may be present to some degree in patients with end-stage kidney disease, especially in those who have osteoporosis that predates the kidney disease. However, after 8 years of hemodialysis and suppression of PTH, the most likely cause of this patient's bone fragility is adynamic bone disease, not osteoporosis.

Educational Objective

Diagnose adynamic bone disease in a patient undergoing dialysis.

17.1. A 37-year-old ♀ is admitted to the hospital with hypercalcemia. Six months ago, she moved from Los Angeles where she worked in the entertainment industry. She has a two-month history of progressive anorexia, 6.8 kg weight loss, nausea, fatigue, polyuria, and polydipsia. She has had no fevers or night sweats. She has no notable medical history and has never had kidney stones, bone pain, or fractures. She takes no medications and states that she has not recently used alcohol, tobacco, or illicit drugs. Exam: she is afebrile, oriented but lethargic, and dehydrated. Findings on breast Exam normal. There is no palpable lymphadenopathy. Nodularity in both buttocks is noted. Lab: Ca: 14.5 mg/dL (8.2-10.2). Albumin 4.1 g/dL (3.5-5). Cr: 2 mg/dL (0.6-1.1). Phosphate 4.9 mg/dL (2.3-4.7). PTH <10 pg/mL (10-65). 25OHD: 15 ng/mL (30-80). 1,25(0H)2D: 82 pg/mL (16-65). CT scan of the buttocks is shown (see image). Which of the following is the most likely diagnosis?

A. Calciphylaxis
B. Fibrodysplasia ossificans progressive
C. Foreign-body granulomas
D. Sarcoidosis
E. T-cell lymphoma

17.2. ANSWER: C) Foreign-body granulomas: This patient has non-PTH-mediated hypercalcemia. In the setting of hypercalcemia and low PTH, 1,25-dihydroxyvitamin D should be suppressed, not elevated. Sarcoidosis (Answer D) and T-cell lymphoma (Answer E) can result in 1,25-dihydroxyvitamin D-mediated hypercalcemia, but this patient's history, physical examination findings, and imaging all point to foreign-body granulomas (Answer C) due to silicone injections as the cause of her hypercalcemia. This suspicion was confirmed by biopsy of one of the nodular masses. Certain lymphomas and granulomas with activated macrophages contain the L-hydroxylase enzyme that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. This activated vitamin D causes hypercalcemia primarily by increasing the gut absorption of calcium (and phosphate), but also by directly causing bone resorption Calciphylaxis (Answer A) occurs in cases where calcium, phosphate, and PTH are all high, and it is associated with necrosis of the skin. Calciphylaxis typically occurs in patients with end-stage kidney disease Fibrodysplasia ossificans progressive (Answer B) is an inherited disorder that does not present with hypercalcemia.

Educational Objective:

Diagnose 1,25-dihydroxyvitamin D-mediated hypercalcemia due to foreign-body granulomas.

18.1. A 48-year-old woman undergoes total thyroidectomy and is left with permanent surgical hypoparathyroidism. She is an avid daily exerciser and experiences muscle cramps unless she takes 1-2 extra Ca chews (400 mg elemental Ca/chew) before and after vigorous exercise. This is in addition to 3000 mg of elemental Ca/day in divided doses; Calcitriol: 1 mcg twice/day; and Levothyroxine, 150 mcg/day. Exam: she has a well-healed thyroidectomy scar and negative Chvostek and Trousseau signs Laboratory test results 6 months after surgery: Serum Ca: 8.2 mg/dL (8.2-10.2). Albumin 4 g/dL (3.5-5). Phosphate 4.9 mg/dL (2.3-4.7). 25OHD: 40 ng/mL (30-80). Urinary Ca: 380 mg/24 h (100-300).

Which of the following should be recommended now?

A. Begin Palopegteriparatide
B. Begin sevelamer
C. Continue current regimen
D. Increase calcitriol by 50%
E. Increase calcium by 50%

18.2. ANSWER: A) 18 Palopegteriparatide:

Patients with hypoparathyroidism cannot stimulate renal tubular reabsorption of filtered calcium due to the lack of PTH effect on the kidneys. Therefore, calcium and calcitriol supplementation in the management of chronic hypoparathyroidism can lead to hypercalciuria, nephrolithiasis, nephrocalcinosis, and kidney insufficiency.

Epidemiologic studies have shown markedly increased relative risks (3- to 6-fold) of kidney dysfunction among those with both surgical and nonsurgical hypoparathyroidism. Because of this, it is important to encourage patients to minimize excessive calcium intake, to take the lowest possible calcitriol dosage, and to try to maintain serum Calcium in the low-normal or even slightly low range. It is also important to monitor urinary calcium excretion and avoid hypercalciuria.

18.2. ANSWER: A) 18 Palopegteriparatide: Because this patient has hypercalciuria, continuing the current regimen (Answer C) is not optimal. Increasing the calcium dosage (Answer E) is not needed since her serum calcium is at target (8-9 mg/dL (2-2.3 mmol/L)) and this would worsen her hypercalciuria. Increasing the calcitriol dosage (Answer D) may allow her to cut down on extra doses of calcium, but it would also increase serum phosphate and hypercalciuria. Sevelamer (Answer B), a phosphate binder, is not indicated for this degree of mild hyperphosphatemia and would not treat her hypercalciuria. Palopegteriparatide (Answer A), taken as a daily self-administered subcutaneous injection, is FDA approved for the treatment of adults with hypoparathyroidism Clinical trials have shown that it can normalize serum calcium in most patients, reduce urinary calcium, and improve quality of life. Patients treated with Palopegteriparatide should be closely monitored, as hypercalcemia and hypocalcemia may occur, and dosage adjustments may be required.

Educational Objective:

Manage chronic surgical hypoparathyroidism.

19.1. A 65-year-old ♀ is referred to the emergency department by her primary care provider for hypercalcemia. She was recently evaluated for fatigue that she had been experiencing for the past 3 months. She has hypertension treated with Amlodipine but otherwise has no notable medical history. She is not taking any additional medications or supplements. She has had no anorexia, nausea, vomiting, abdominal pain, polyuria, polydipsia, or other new symptoms

Exam: demonstrates pallor of the mucus membranes. She is alert and oriented to person, place, and time.

Lab: Serum Ca: 18.4 mg/dL (8.2-10.2). Ionized Ca: 4.9 mg/dL (4.6-5.08). PTH: 23 pg/mL (10-65). 25OHD: 22 ng/mL (30-80). Albumin 3.9 g/dL (3.5-5). Hemoglobin 9.9 g/dL (12.1-15.1). Cr: 1.5 mg/dL (0.6-1.1).

Serum protein electrophoresis, high level of monoclonal protein.

Which is the best next step to treat this patient's elevated calcium?

A. Cinacaket, 30 mg orally 3 times daily
B. Emergency plasmapheresis
C. Normal saline intravenously
D. No treatment necessary
E. Pamidronate, 60 mg intravenously

19.2. ANSWER: D) No treatment necessary. Fifty percent of circulating calcium is bound to serum proteins, primarily to albumin. In this patient with multiple myeloma, the serum albumin is normal. However, in some patients with multiple myeloma, high circulating levels of serum immunoglobulins can also bind calcium, leading to pseudohypercalcemia. The key to recognizing this condition is to note the marked discrepancy between the serum calcium (very high) and the patient's symptoms (almost none). No therapy is needed (Answer D). Normal saline intravenously (Answer C), cinacalcet therapy (Answer A), pamidronate therapy (Answer E), and emergency plasmapheresis (Answer B) are reasonable steps in the treatment of true, severe hypercalcemia, but they are not needed in this case.

Educational Objective:

Diagnose pseudohypercalcemia and guide management.

20.1. A 74-year-old ♂ with osteoporosis has been on oral alendronate, 70 mg weekly, for 5 years. He has no known history of fracture. Current DXA shows T-scores of -2 at the lumbar spine, -2.2 at the femoral neck, and -1.6 at the total hip. Exam: height: 170 cm: a decrease of 6.4 cm over the past 4 years. He has moderate kyphosis without tenderness. Gait and balance are normal. Lab: Serum Ca: normal. Phosphate: normal. Cr: normal. 25OHD: normal. Testosterone: lower end of reference range. He expresses concerns about long-term adverse effects from bisphosphonates. Which is the best next step in this patient's management?

A. Continue oral alendronate
B. Discontinue alendronate but reassess in 1 to 2 years
C. Measure fasting serum C-telopeptide
D. Obtain lateral spine radiographs
E. Obtain radiographs of both proximal femurs

20.2. ANSWER: D) Obtain lateral spine 20 radiographs

A frequent clinical question is when or if to give a "bisphosphonate holiday" to patients with osteoporosis who have been on either oral or intravenous bisphosphonates for several years. Because bisphosphonates have long retention in the skeleton, they may continue to exhibit antifracture efficacy even after therapy is stopped. The decision to stop bisphosphonate therapy must be individualized. Studies have shown that after 3 years of annual intravenous zoledronic acid or 5 years of oral bisphosphonate therapy, it is reasonable to reassess each patient and determine Whether a bisphosphonate holiday may be considered. Patients and physicians worry about the risk of rare but devastating adverse effects (such as osteonecrosis of the jaw and atypical femoral fractures) that seem to be correlated with duration of bisphosphonate therapy.

20.3. ANSWER: D) Obtain lateral spine 20 radiographs

Data from the FLEX and HORIZON
extension trials show that many patients can stop bisphosphonate therapy temporarily after 3 to 5 years without loss of bone mineral density or increased fracture risk. However, some subgroups of patients appear to be at higher risk for bone loss or fractures after stopping therapy. For these patients, the options include either continuing the bisphosphonate for up to 10 years with periodic reassessment or stopping the bisphosphonate and switching to a different agent. Patients at higher risk include those with a history of hip or vertebral fractures, multiple fractures, a T-score of -2.5 or lower at the hip, or other factors placing them "at high risk" for fractures
The best next step in this case is to obtain lateral spine radiographs (Answer D).

20.4. ANSWER: D) Obtain lateral spine 20 radiographs

Routine radiographs of the proximal femurs (Answer E) are not recommended as part of the evaluation of asymptomatic patients on bisphosphonate therapy. He has apparently had a good response to treatment and has not sustained a known clinical fracture. Thus, he might qualify for a "bisphosphonate holiday" (Answer B). However, the loss of height over the past 4 years and moderate kyphosis suggest that he may have one or more unrecognized vertebral fractures that change the diagnosis to severe osteoporosis and move him into a very high fracture risk category The presence of a prevalent vertebral fracture would prompt either continued antiresorptive therapy with a bisphosphonate for up to 10 years (such as alendronate [Answer A]) or a switch to denosumab or an anabolic agent (teriparatide and abaloparatide are approved in the US for treatment in men, and romosozumab is approved for men in some countries).

20.5. ANSWER: D) Obtain lateral spine 20 radiographs

Radiographs are recommended for asymptomatic individuals with height loss and/or kyphosis because up to 70% of vertebral fractures are clinically silent. While many clinicians use measurement of fasting serum C-telopeptide (Answer C) to determine whether or when patients should discontinue bisphosphonates and whether or when they should resume therapy, there are no data to support this approach. Finally, it is important to note that not all bisphosphonates are the same. Alendronate and zoledronic acid have much longer retention in bone than do ibandronate or risedronate. With the latter two bisphosphonates, decreases in bone density can occur within 6 to 12 months—therefore, drug holidays, if given at all, must be short.

Educational Objective:

Assess the appropriateness of "bisphosphonate holidays" in osteoporosis management.

21.1. A 74-year-old is admitted to Hospital 21 with altered mental status, nausea, vomiting, and dehydration. His medical history is notable for chronic obstructive pulmonary disease, coronary artery disease, and an 80-pack-year smoking history.
Exam: he is barely aroused. BP: 96/65, Pulse: 120. He has dry mucous membranes, and there is no lymphadenopathy. Chest x-ray in the emergency department reveals a 3-cm spiculated mass in right upper lung lobe + destruction of adjacent rib.
Lab: Ca: 16.8 mg/dL (8.2-10.2). Ionized Ca: 7.25 mg/dL (4.60-5.08). Urea: 50 mg/dL (8-23). Cr: 2.5 mg/dL (0.7-1.3). Serum protein electrophoresis: normal. Urine protein electrophoresis: normal. Intact PTH: <10 pg/mL (10-65). The patient receives vigorous IV saline hydration (2 L in the first 4 hours followed by 150 cc/h) with subsequent improvement in Cr. He also receives Calcitonin 4 units/kg every 6 hours; and Zoledronic acid 4 mg IV (1 dose). 48 hours after admission, he is more alert and responsive. BP: 140/85, Pulse: 90. Serum Ca now 13.8 mg/dL (3.5 mmol/L), and Cr 1.4 mg/dL. Which of the following is the best next step?

A. Administer another dose of zoledronic acid, 4 mg intravenously
B. Administer denosumab, 60 mg subcutaneously
C. Begin hydrocortisone, 50 mg intravenously every 6 hours
D. Increase the rate of intravenous saline to 200 cc/h and add furosemide
E. Stop calcitonin and continue current hydration and monitoring

21.2. ANSWER: E) Stop calcitonin and continue current hydration and monitoring

This is a classic case of humoral hypercalcemia of malignancy leading to a hypercalcemic crisis. The underlying etiology is secretion of PTHrP from squamous cell carcinoma of the lung. Hypercalcemic crisis is defined as a corrected serum calcium value of 14 mg/dL (3.5 mmol/L) or higher with rapid deterioration of multiple organs (e.g., central nervous system, cardiac, gastrointestinal, and kidney). Acute management of hypercalcemic crisis involves saline hydration, subcutaneous calcitonin for 24-48 hours, intravenous bisphosphonate (or subcutaneous denosumab in selected cases), and treatment of the underlying disease.

Furosemide (Answer D) should be added only when there is clinical evidence of volume overload or congestive heart failure. In the case of VD-mediated hypercalcemia, prednisone 40-60 mg/day, or another glucocorticoid equivalent (Answer C), may be useful, but it should not be given without biochemical evidence of inappropriate VD levels.

21.3. ANSWER: E) Finally, in patients with hypercalcemic crisis due to primary hyperparathyroidism, cinacalcet can be a "bridge" to parathyroidectomy. The peak hypocalcemic action of intravenous bisphosphonate starts around 48 hours after administration and peaks around day 6. Because this patient is clinically improving after only 48 hours, the best next step is to stop calcitonin and continue current hydration and monitoring (Answer E). To give another dose of zoledronic acid (Answer A) so quickly would be unnecessary and could potentially lead to prolonged hypocalcemia. Denosumab (Answer B) is also approved for the treatment of hypercalcemia from solid tumors, but it would not be needed now for the same reason. Ultimately, the key to treating malignant hypercalcemia is to treat the underlying cancer with surgery, chemotherapy, and other modalities.

Educational Objective:

Manage hypercalcemic crisis in a patient with humoral hypercalcemia of malignancy

22.1. A 71-year-old ♂ is referred after DXA documented a femoral neck T-score of -2.9. His only other medical issue is mild benign prostatic hypertrophy. He has a healthy sex drive and no problems achieving or maintaining erections for intercourse. His overall strength and energy are good, and he is still working full time. His current height is 3.8 cm less than his peak height

Exam: BMI: 24 kg/m^2. He has no kyphosis and there is room for 2 fingers in the space between the ribs and iliac crests in the midaxillary line.

Lab: CBC: normal. Chemistry panel: normal. 25OHD: 35 ng/mL (30-80). Urinary Ca excretion 285 mg/24 h (100-300). Serum testosterone (8 AM) 285 ng/dL (300-900). SHBG: normal. LH 6 mIU/mL (1-9). Prolactin 6 ng/mL (4-23). PSA 6.5 ng/mL (< 7). Which treatments should be recommended?

A. Alendronate
B. Hydrochlorothiazide
C. Teriparatide
D. Testosterone gel
E. Testosterone gel + Finasteride

22.2. ANSWER: A) Alendronate. This patient has no symptoms of Testosterone deficiency and no indication that his mildly low testosterone is "organic." Because there are no large randomized controlled trials showing antifracture effectiveness for testosterone in men with osteoporosis, testosterone therapy (Answers D and E) should only be considered for hypogonadal men who are symptomatic, have an organic cause for the hypogonadism, have testosterone levels less than 200 ng/dL (<6.9 nmol/L), and/or are not candidates for other therapies. If he was symptomatic or had lower testosterone levels, testosterone therapy with a 5α-reductase inhibitor such as finasteride could be given without exacerbating his benign prostatic hypertrophy. However, even men with marked hypogonadism respond well to antiosteoporosis therapy without correction of the hypogonadism. He should be offered treatment with an agent approved to treat osteoporosis in men and one that reduces fracture risk, such as alendronate (Answer A). Teriparatide (Answer C) is generally not a first-line agent for osteoporosis and is best reserved for those with vertebral fractures or very low bone mineral density. Hydrochlorothiazide (Answer B) can be used for the management of hypercalciuria, but this patient has urinary calcium excretion within the reference range for men.

Educational Objective:

Recommend appropriate management of male osteoporosis in the setting of borderline-low testosterone

23.1. A 65-year-old postmenopausal ♀ with stage 1 breast cancer and no evidence of metastatic disease has completed surgery and radiation therapy to the breast. She has no history of fractures. Her oncologist would now like to treat her with anastrozole (an aromatase inhibitor) for at least 5 years. The oncologist orders a DXA, which demonstrates T-scores of -2.2 at the lumbar spine, -1.7 at the femoral neck, and -1.5 at the total hip. Vertebral fracture assessment is negative for fracture. The FRAX results do not meet treatment thresholds for either major osteoporotic fractures or hip fractures. The oncologist refers the patient for advice regarding bone health In addition to optimizing Ca and VD, which interventions should be recommended?

A. Calcitonin
B. No intervention needed
C. Raloxifene
D. Teriparatide
E. Zoledronic acid

23.2. ANSWER: E) Zoledronic acid

Several clinical trials have demonstrated that women with breast cancer treated with aromatase inhibitors experience higher rates of bone loss and fragility fractures, particularly in the first 1 to 2 years of therapy, compared with rates in women treated with tamoxifen. Thus, recommending no intervention (Answer B) is incorrect. Current recommendations are to optimize calcium and vitamin D supplementation and perform DXA screening. International guidelines recommend antiresorptive treatment for patients initiating aromatase inhibitor therapy with a T-score of -2.0 or less, regardless of additional risk factors, for the duration of aromatase inhibitor treatment. In addition, patients with any two of the following risk factors should receive antiresorptive therapy: T-score of -1.5 or less, age greater than 65 years, low BMI (<20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use of greater than 6 months, and current cigarette smoking (or history of smoking).

23.3. ANSWER: E) Zoledronic acid: Several large clinical trials in postmenopausal women with early-stage breast cancer have shown that aromatase inhibitor-induced bone loss can be prevented by treatment with antiresorptive agents at the onset of aromatase inhibitor therapy. The drug regimen that has been studied most extensively is intravenous zoledronic acid (4 mg every 6 months) (Answer E). Oral bisphosphonates can also be used in this setting, although clinical trial data are not nearly as extensive. Denosumab, 60 mg SC every 6 months, has also been shown to reduce both Fractures and cancer recurrence in postmenopausal women with early-stage breast cancer. Calcitonin (Answer A) is a weak antiresorptive agent that would not be appropriate in this patient. Teriparatide (Answer D) is contraindicated in patients with a history of radiation therapy due to an increased risk of osteosarcoma. Raloxifene (Answer C), a selective estrogen receptor modulator, significantly reduces estrogen receptor-positive breast cancer in women with osteoporosis, but it is not approved for use in women with a diagnosis of breast cancer.

Educational Objective:

Manage low bone mass in the setting of breast cancer and aromatase inhibitor therapy

24.1. An 82-year-old ♀ is admitted to the hospital with diffuse bony pain and a pathologic, atraumatic fracture of her left distal radius. She has not had regular medical care. Radiographs reveal widespread lytic and mixed (lytic/sclerotic) lesions throughout the appendicular and axial skeleton.

Exam: a large breast mass is palpated, and needle biopsy confirms adenocarcinoma of the breast.

Lab: Serum Ca: 12.3 mg/dL (8.2-10.2). Albumin: 2.8 g/dL (3.5-5). Cr: 6.2 mg/dL (0.6-1.1). PTH < 10 pg/mL (10-65). 25OHD: 8 ng/mL (30-80). ALP: 320 U/L (50-120). After 24 hours of vigorous IV saline hydration, the following lab documented: Serum Ca: 11 mg/dL. Cr: 4.2 mg/dL. The oncology team decides to treat her with SC injection of Denosumab 120 mg. In this patient, which is the most likely adverse effect of this therapy?

A. Impaired fracture healing
B. Osteonecrosis of the jaw
C. Severe flu-like syndrome
D. Severe hypocalcemia
E. Worsening kidney function

24.2. ANSWER: D) Severe hypocalcemia

Denosumab, a fully human monoclonal antibody against RANK ligand, is approved for the treatment of osteoporosis, as well as metastatic solid tumors, such as breast cancer. It is a very potent inhibitor of osteoclastic bone resorption. Unlike bisphosphonates, denosumab is not cleared via the kidneys and has no effect on kidney function (Answer E). Although cases of osteonecrosis of the jaw (Answer B) have been reported with both bisphosphonates and denosumab, this is very unlikely after only a single dose of the drug. Severe flulike syndromes (Answer C) (also known as "acute phase reactions") are much more common with intravenous bisphosphonates than with denosumab. Potent antiresorptive agents such as denosumab have not been shown to impair fracture healing (Answer A). The major possible adverse effect of denosumab in patients with severe chronic kidney disease is profound, symptomatic hypocalcemia (Answer D) within 7-10 days following administration.

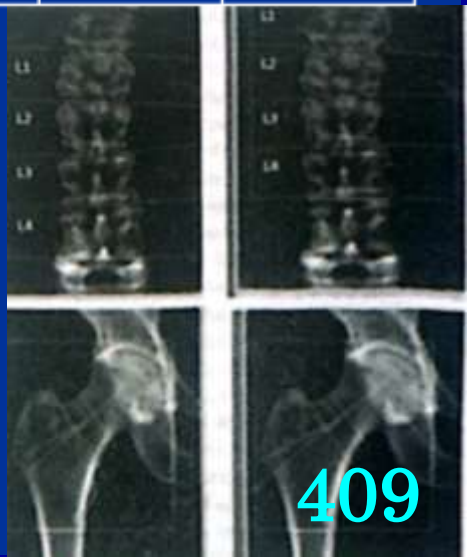
24.3. ANSWER: D) Severe hypocalcemia: Patients at greatest risk for this complication are those with very low kidney function, high bone turnover with elevated alkaline phosphatase, and low baseline albumin-corrected serum Ca. The potent inhibition of osteoclastic bone resorption by denosumab stops the efflux of Ca from bone and can dramatically lower serum calcium. The usual physiologic responses to hypocalcemia, such as a rise in PTH and calcitriol production, which would normally lead to increased renal tubular reabsorption of Ca and increased gut absorption of Ca, will not work in the setting of kidney failure. This woman also has a very low VD level. Therefore, even if kidney function were better, she would still be at risk for an inadequate homeostatic response due to the very low VD substrate Her high baseline serum Ca is likely to mitigate the possibility of postdenosumab hypocalcemia.

Educational Objective:

Anticipate the risk of symptomatic hypocalcemia following Denosumab in the setting of kidney failure.

25.1. A 62-year-old ♀ with osteoporosis She has been taking risedronate, 35 mg weekly, for the past two years. She has adhered to this regimen, except for two missed doses. She has not experienced any adverse effects. Repeated bone density testing is performed at the same center as her initial study. The report indicates a significant loss of bone mineral density in the spine and increases in bone mineral density in the femoral neck and total hip. The DXA images and numerical results are shown (see images and table).

Site	Baseline bone mineral density	Follow up bone mineral density
L1	0.451	0.423
L2	0.548	0.449
L3	0.593	0.549
L4	0.617	0.591
Total L1-L4	0.557	0.507
Femoral neck	0.489	0.532
Total HIP	0.590	0.595



Which is the best explanation for these findings?

A. Analysis of lumbar spine bone mineral density was incorrect
B. Her hip bone mineral density was measured incorrectly
C. She has an underlying cause of secondary osteoporosis
D. She is not responding to risedronate
E. She is not taking risedronate correctly

25.2. ANSWER: A) Analysis of lumbar 25 mm spine bone mineral density was incorrect

It is always important to look at the images and numbers of a DXA study, particularly when the results do not make sense. Although gains in bone mineral density at one site and loss at another are possible, this situation is very uncommon. In this patient's images, the labeling of the lumbar spine vertebral bodies was inconsistent, one level higher than in the previous study (i.e., L4 in the current study is actually L3) (Answer A). After correcting the analysis error, she had a significant 2.1% improvement in spine bone mineral density.

Her hip images are correct (thus, Answer B is incorrect).

She appears to be responding to risedronate (thus, Answer D is incorrect), and therefore she is most likely taking it correctly (thus, Answer E is incorrect). The gains seen in the hip are higher than the least significant change assumed to be 2.8% for the total hip and 5% for the femoral neck in clinical DXA studies.

There is no reason to suspect that she has an undiagnosed secondary cause of osteoporosis (Answer C).

Educational Objective:

Carefully review DXA images and identify common technical errors.

26.1. A 74-year-old woman with severe O-3.2, compression fractures of T8 and T9 after minimal or no trauma has been self-injecting teriparatide, 20 mcg daily, for the past 3 months every morning. She has been on hydrochlorothiazide/triamterene, 25/37.5 mg daily, for hypertension for many years. She gets 600 mg of Ca from food sources daily and takes a Ca supplement, 600 mg once/day with food. Before starting teriparatide, baseline serum Ca was normal. On the day of her visit, she skips her morning Teriparatide injection and comes to the clinic in the late afternoon. She feels well. BP: 138/90. Lab: (36 hours after last teriparatide injection): Serum Ca: 10.6 mg/dL (8.2-10.2). Albumin 3.9 g/dL (3.5-5). Urea: 12 mg/dL (8-23). Cr: 0.9 mg/dL (0.6-1.1). In addition to rechecking laboratory values within 1-2 weeks, which of the following should be advised?

A. Decrease the hydrochlorothiazide dosage to 12.5 mg daily
B. No changes needed
C. Stop calcium supplement
D. Stop hydrochlorothiazide
E. Stop teriparatide

26.2. ANSWER: C) Stop the calcium supplement

Serum calcium is often slightly (and transiently) elevated in the hours immediately following the day's dose of teriparatide, but it will usually be back within normal limits on samples drawn 16 or more hours after the last dose. Patients who take teriparatide in the morning and need blood work done should be told to delay their teriparatide dose until after samples for lab tests have been drawn, as this patient did. But her serum calcium is still high, suggesting that a change in therapy is needed (thus, Answer B is incorrect). Due to high bone turnover and calcium flux, some patients do have mild hypercalcemia during the first 3 to 6 months after starting teriparatide. Because she is asymptomatic and the calcium elevation is mild, it is reasonable to first stop her calcium supplement (Answer C) with the understanding that this will be restarted again in the future. There is no indication to stop hydrochlorothiazide (Answer D) or decrease the dosage (Answer A), as she has been on this. She has been taking teriparatide for many years and remains mildly hypertensive. Stopping teriparatide now (Answer E) is not necessary unless she remains persistently hypercalcemia.

Educational Objective:

Manage mild hypercalcemia during teriparatide therapy for osteoporosis.

27.1. A 69-year-old ♀ has been treated with Alendronate, 70 mg/week, for 2 years. Recent DXA shows a femoral neck T-score of -2.7 and no change in bone mineral density compared with findings from 2 years ago. She says she is 7.6 cm shorter than her young adult height, but she does not know whether her height has changed over the past few years. Vertebral fracture assessment shows a compression fracture of L1 (see image). No baseline testing is available For the past several years, she has had back pain almost every day, some days more than others, but she does not recall an incident that might explain this finding. Which tests is most likely to give useful information regarding the age of this fracture if it occurred more than 6 months ago?

A. Bone-specific alkaline phosphatase measurement
B. CT
C. Lumbar spine radiograph
D. MRI
E. Nuclear medicine bone scan

27.2. ANSWER: E) Nuclear medicine bone scan

This patient cannot recall any circumstances that might account for the fracture. In this case, it would be useful to know whether the fracture occurred within the past 2 years. A nuclear medicine bone scan (Answer E) would show uptake for 1 to 2 years after a fracture

Although it is common to detect vertebral fractures on radiographs, and radiographs may be more sensitive than vertebral fracture assessment for finding subtle fractures (grade 1), the age of the fracture cannot be determined from a radiograph (Answer C).

Bone turnover markers, such as bone-specific alkaline phosphatase (Answer A), increase as part The elevation of the vertebral fracture may remain high for 6 to 12 months, but its magnitude and duration are not well characterized. MRI (Answer D) shows marrow edema soon after a fracture, but this usually resolves within 2 to 3 months. MRI or CT (Answer B) may be useful to rule out malignancy as a cause of the fracture. CT is fine for morphometry (determining whether there is a fracture), but it is not as good as MRI for dating acute fractures. A fracture is not an indication of treatment failure; however, it is certainly not the desired outcome, and changing medications would be reasonable. A recent fracture (in the previous 1 to 2 years) is associated with a much higher risk of future fracture and causes greater clinical concern than a remote fracture.

Educational Objective:

Choose a nuclear medicine bone scan over MRI to determine the age of a vertebral fracture

28.1. A 57-year-old ♂ has his third 28-episode episode of nephrolithiasis. Analysis of the stone shows Ca oxalate. Evaluation demonstrates normal serum Ca and PTH levels, with a 24-hour urinary Ca excretion of 335 mg/24 h (100-300) (SI: 8.4 mmol/d (2.5-7.5 mmol/d)), but normal 24-hour urinary oxalate, uric acid, sodium, and citrate levels. Urine volume is 2600 mL/24 h. His diet contains about 1000 mg of elemental Ca/day. Which recommendations would provide the greatest reduction in his risk of future Ca oxalate stone disease?

A. Begin allopurinol
B. Begin hydrochlorothiazide
C. Increase fluid intake
D. Reduce dietary calcium
E. Reduce dietary oxalate

28.2. Answer: B) Begin Hydrochlorothiazide

In patients with multiple stone episodes—most of whom have already increased their fluid intake—thiazide diuretics (Answer B) and citrate supplements are similarly effective in patients with hypercalciuria, as well as in unselected patients. Hydrochlorothiazide acts to enhance renal calcium reabsorption to reduce urinary calcium excretion. Citrate acts as a stone inhibitor. Reducing dietary calcium (Answer D) is counterproductive since dietary calcium binds with dietary oxalate and helps reduce intestinal oxalate absorption Hypercalciuria may be caused by increased sodium intake, which leads to increased sodium excretion and an obligatory loss of calcium in the urine; however, this patient's urinary sodium excretion is normal, as is his urinary uric acid level. Thus, prescribing allopurinol (Answer A) is incorrect. His urinary oxalate level is normal, so there would be no benefit in reducing dietary oxalate (Answer E). Finally, the urine volume of 2.6 L suggests that increased fluid intake (Answer C) would not be helpful. The goal is to aim for a urine volume greater than 2.5 L per day. Other risk factors for recurrent kidney stones include excessive intake of salt and proteins and a high dietary acid load. The intake of vegetables and a vegetarian-type diet is encouraged in stone-forming patients. Consumption of sugar-sweetened soda is associated with a higher risk of stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice is associated with a lower risk

Educational Objective:

Recommend a thiazide diuretic to reduce the risk of recurrent kidney stones

29.1. A 63-year-old postmenopausal ♀ with osteoporosis and rheumatoid arthritis affecting her hands has been on prednisone, 5 mg daily, and alendronate 70 mg weekly, for the past 2 years. Recently, temporal arteritis was diagnosed, and her prednisone dosage was increased to 20 mg/day. One month later, she sustained a painful vertebral fracture during a yoga class. She is very adherent to her treatment regimen of Alendronate, Ca, and VD. A workup for secondary causes of vertebral fracture is negative. DXA documents T-scores of -2.6, -1.8, and -1.4 at the lumbar spine, total hip, and femoral neck, respectively. Bone mineral density at the spine has improved 4% over the past 2 years. Which is the best recommendation now?

A. Continue alendronate
B. Continue alendronate and add teriparatide
C. Switch to denosumab
D. Switch to teriparatide
E. Switch to zoledronic acid

29.2. ANSWER: D) Switch to teriparatide.

The American College of Rheumatology 2022 guidelines on glucocorticoid-induced osteoporosis give a conditional recommendation for treatment with a PTH analogue over a bisphosphonate or denosumab in patients at very high fracture risk, and a strong recommendation for bisphosphonate or denosumab over no treatment. The US FDA has approved alendronate, risedronate, zoledronic acid, denosumab, and teriparatide for the management of glucocorticoid-induced osteoporosis. Due to cost, effectiveness, and ease of use, alendronate or risedronate are often the first-line treatment. However, evidence for persistent efficacy of oral bisphosphonates in glucocorticoid-induced osteoporosis after 2 years is very limited. Given this patient's higher prednisone dosage and the spontaneous vertebral fracture while on alendronate, a change in therapy is reasonable. Thus, simply continuing therapy (Answer A) is incorrect.

Zoledronic acid (Answer E) is unlikely to be any more effective in someone who is adhering to oral bisphosphonate therapy.

29.3. ANSWER: D) Switch to teriparatide. Denosumab (Answer C) could be expected to increase bone density more than bisphosphonates, but it shares with these the limitation of not addressing the major mechanism of glucocorticoid-induced osteoporosis-reduced bone formation. Teriparatide (Answer D) is currently the only anabolic agent approved for glucocorticoid-induced osteoporosis. In a randomized controlled trial, teriparatide was found to be superior to alendronate and risedronate in terms of bone mineral density and vertebral fracture reduction. In unrelated trials For glucocorticoid-induced osteoporosis, combination therapy with teriparatide and alendronate together (Answer B) blunts the efficacy of teriparatide, although some dispute this and recommend continuing alendronate when adding teriparatide. Currently, combination therapy is not generally recommended outside of clinical trials or in exceptional circumstances.

Educational Objective:

Manage a vertebral fracture in a patient with glucocorticoid-induced osteoporosis taking alendronate.

30.1. A 40-year-old ♂ is referred for 30-day management of osteogenesis imperfecta. This condition was diagnosed in childhood after he sustained multiple fractures, and he was treated with intermittent intravenous pamidronate until his late teenage years. His main concern is worsening bone pain and several recent extremity fractures with minor trauma. Current DXA reveals T scores of -3 at the lumbar spine, -3.2 at the femoral neck, and -3.5 at the total hip.

Exam: he has short stature (height 152 cm). Sclerae are blue. He has multiple joint deformities and dentinogenesis imperfecta. He wears bilateral hearing aids. Bisphosphonate therapy is restarted. Which benefits is most likely to occur with bisphosphonate therapy in this patient?

A. Decreased bone pain
B. Decreased fracture risk
C. Increased bone mineral density
D. Improved dentition
E. More rapid fracture healing

30.2. ANSWER: C) Increased bone mineral density

Osteogenesis imperfecta (or "brittle bone disease") is a rare, inherited disorder of type 1 collagen. Ninety percent of cases result from pathogenic variants in the genes encoding type 1 collagen (COLIA1/COLIA2). The main therapy for osteogenesis imperfecta remains bisphosphonates (Intravenous pamidronate and zoledronic acid and oral bisphosphonates). The most consistent benefit in affected adults who receive bisphosphonates is increased bone mineral density (Answer C). Children with osteogenesis imperfecta who receive bisphosphonate therapy can experience decreased bone pain (Answer A) and decreased fracture risk (Answer B), but these outcomes are not definitive for adults. Improved dentition (Answer D) and more rapid fracture healing (Answer E) are not seen with bisphosphonate therapy in adults with osteogenesis imperfecta.

Educational Objective:

Describe the role of bisphosphonate therapy for adults with osteogenesis imperfecta.

31.1. An 88-year-old ♂ is admitted to the 31st with vesical muscle twitching and multiple falls. His history is notable for congestive heart failure. Last year he was hospitalized with bleeding gastric ulcers due to heavy use of nonsteroidal anti-inflammatory drugs and was started on omeprazole, 40 mg three times daily. Current medications include furosemide, 40 mg daily, and omeprazole, 40 mg twice daily. Exam: he is a thin, elderly man with markedly positive Chvostek and Trousseau signs.
Lab: Serum Ca: 6.8 mg/dL (8.2-10.2). Ionized Ca: 3 mg/dL (4.60-5.08). Phosphate: 4.7 mg/dL (2.3-4.7). Cr: 0.9 mg/dL (0.7-1.3). PTH: 30 pg/mL (10-65). Measurement of which is most likely to explain this patient's presentation?

A. 1,25-Dihydroxyvitamin D
B. Serum magnesium
C. Tissue transglutaminase antibodies
D. 25-Hydroxyvitamin D
E. 24-Hour urinary calcium excretion

31.2. ANSWER: B) Serum magnesium. This elderly man presents with symptoms of tetany and biochemical evidence of hypoparathyroidism. In the setting of severe hypocalcemia, an intact PTH value within the normal range is inappropriate, as it should be frankly elevated. The most likely etiology for this patient's subacute hypoparathyroidism is magnesium deficiency (Answer B) due to proton-pump inhibitor therapy. The association between proton-pump inhibitor therapy and hypomagnesemic hypoparathyroidism was first reported in 2006. Although it is still a relatively rare syndrome, individuals at the highest Those at risk appear to be on proton-pump inhibitor therapy for one year or longer, elderly persons, and those on concurrent diuretics. This phenomenon appears to be a class effect that can occur with any of the available proton-pump inhibitors. The underlying mechanism is unclear, but proton-pump inhibitors most likely affect gastrointestinal absorption of magnesium. Hypocalcemia secondary to hypomagnesemia is due to functional hypoparathyroidism, as PTH release is a magnesium-dependent process.

31.2. ANSWER: B) Serum magnesium. This type of hypocalcemia is typically refractory to correction until the magnesium deficit has been corrected. A second mechanism of hypocalcemia in the setting of proton-pump inhibitor use relates to the decrease in calcium bioavailability in the presence of gastric achlorhydria, given that calcium absorption is a pH-dependent process. Measurement of 25-hydroxyvitamin D (Answer D) or 24-hour urinary calcium excretion (Answer E) would be useful in cases of hypocalcemia and secondary hyperparathyroidism where vitamin D deficiencies and low urinary calcium excretion would be expected.

A search for causes of malabsorption, such as occult celiac disease, with assessment for tissue transglutaminase antibodies (Answer C) would be appropriate in secondary hyperparathyroidism. Levels of 1,25-dihydroxyvitamin D (Answer A) can be normal, low, or high in hypocalcemic patients depending on the substrate, kidney function, and PTH levels, so its measurement is not helpful.

Finally, it should be noted that proton-pump inhibitors have been associated with an increased risk of falls, bone loss, and fractures.

Educational Objective

Diagnose hypomagnesemic hypoparathyroidism associated with proton-pump inhibitor use

32.1. A 75-year-old ♀ had a humerus 32 fracture after a fall from standing height. She has no notable medical history other than borderline hypertension. Recent DXA was significant for T-scores of -2.1 at the lumbar spine, -1.9 at the femoral neck, and -1.7 at the total hip. She is a former cigarette smoker. She has no parental history of hip fracture. She takes a daily supplement with 1200 mg of Ca in divided doses and 800 IU (20 mcg) of VD. Which is the best recommendation for this patient regarding pharmacologic osteoporosis therapy?

A. Not needed because she has osteopenia, not osteoporosis
B. Strongly recommended based on her age
C. Strongly recommended because of her humerus fracture
D. Strongly recommended because of her history of tobacco use
E. Treatment only if her FRAX-derived 10-year risk of major osteoporotic fracture is ≥20% or hip fracture risk is 23%

32.2. ANSWER: C) Strongly recommended because of her humerus fracture

Osteoporosis is a skeletal disorder classified by increased fracture risk. According to the American Association of Clinical Endocrinology guidelines, as well as others, osteoporosis can be diagnosed after a fragility fracture, regardless of T-score, or by a T-score equal to or less than -2.5 in the hip, spine, or forearm. This patient has osteoporosis, diagnosed by her humerus fracture (thus, Answer A is incorrect), and treatment is strongly recommended (Answer C). Many patients with fragility fractures, including hip fractures, have a T-score that is greater than -2.5.

Use of the FRAX tool to decide on this patient's treatment (Answer E) is inappropriate.

Age alone (Answer B) is not a reason to recommend treatment.

While current tobacco use is a risk factor for fracture as per FRAX, prior tobacco use (Answer D) is not considered a risk

Educational Objective:

Diagnose osteoporosis on the basis of a fragility fracture

33.1. A formerly healthy 48-year-old ♂ is referred for evaluation and management of muscle pain, fatigue, and weakness that began 18 months ago. Exam: he has proximal muscle weakness and tenderness to palpation over the anterior tibia. Lumbar spine Z-score is -3.3.
Lab: Chemistry panel: normal. 25OHD: 28 ng/mL (30-80). 1,25(OH)2D: 12 pg/mL (16-65). PTH-98 pg/mL (10-65). Serum and urine protein electrophoresis, free kappa and lambda light chains: normal. Serum phosphate ranges between 1.1-1.3 mg/dL (2.3-4.7).
Serum FGF23: 350 RU/mL (< 180 RU/mL)
Which treatments should be recommended now?

A. Alendronate
B. Cholecalciferol and calcitriol
C. Potassium phosphate alone
D. Potassium phosphate and calcitriol
E. Zoledronic acid

33.2. ANSWER: D) Potassium phosphate and calcitriol: This patient most likely has tumor-induced osteomalacia caused by a benign mesenchymal tumor that is secreting FGF-23, which causes renal tubular loss of phosphorus and inhibits β-hydroxylase, resulting in low 1,25-dihydroxyvitamin D levels. Treatment should include both potassium phosphate and calcitriol (Answer D). Potassium phosphate alone (Answer C) could result in secondary hyperparathyroidism since phosphate loading reduces serum calcium, thereby stimulating PTH release. Treating with only cholecalciferol and calcitriol (Answer B) would not correct the hypophosphatemia. These tumors are typically located in the skin, bones, or connective tissue (e.g., sinuses) and may be difficult to localize. Imaging to localize the tumor includes nuclear medicine imaging techniques, such as bone scan, octreotide scan, or PET. In difficult cases, serum FGF-23 on selective venous sampling may be used to localize the extremity from which FGF-23 is being secreted. Tumor removal (if it can be located and removed) normalizes renal phosphate handling within hours to days. Burosumab has been approved for FGF-23-related hypophosphatemia in tumor-induced osteomalacia associated with mesenchymal tumors that cannot be localized or curatively resected in adults and children 2 years and older. Neither alendronate (Answer A) nor zoledronic acid (Answer E) would improve his serum phosphate or osteomalacia and might actually be harmful.

Educational Objective:

Recommend appropriate treatment of hypophosphatemia due to tumor-induced osteomalacia

34.1. A 20-year-old homeless ♀ is taken to the emergency department for evaluation. She is unable to give a clear history due to mild intellectual disability, but she does describe numbness and tingling of her hands. Lab: Ca: 6 mg/dL (8.2-10.2). Albumin 3 g/dL (3.5-5). Phosphate: 5.9 mg/dL (2.3-4.7). PTH: 420 pg/dL (10-65). 25OHD: 16 ng/mL (30-80). TSH: 5.9 mIU/L (0.5-5). FT4: 0.9 ng/dL (0.8-1.8). Which is this patient's most likely diagnosis?

A. Activating pathogenic variant in the gene encoding the calcium-sensing receptor (CASR)
B. Autoimmune polyglandular syndrome type 1
C. DiGeorge syndrome (22q11.2 deletion syndrome)
D. Pseudohypoparathyroidism type 1A
E. Pseudopseudohypoparathyroidism

34.2. Answer D) Pseudohypoparathyroidism Type 1A

This young woman has classic signs of pseudohypoparathyroidism type 1A (Answer D). Pseudohypoparathyroidism is a group of disorders defined by end-organ resistance to PTH that results in hypocalcemia, hyperphosphatemia, and elevated PTH levels. The syndrome is caused by pathogenic variants in the GNAS gene that encodes a subunit of the G protein, which is linked to the PTH receptor. Pathogenic variants prevent the generation of adenyl cyclase when PTH binds to its receptor and therefore, failure of signal transduction by PTH. Interestingly, GNAS is imprinted in humans, so that the expression of the allele for a specific tissue depends on whether the allele is inherited from the mother or the father Thus, pseudohypoparathyroidism type 1A is an autosomal dominant disease with a loss-of-function variant in GNAS that manifests only when the variant is inherited from the mother. Affected patients have the biochemical abnormalities listed above, as well as a classic phenotypic appearance known as Albright hereditary osteodystrophy.

34.3. Answer D) Pseudohypoparathyroidism Type 1A: Such patients have rounded facies, short stature, obesity, developmental delay, and short fourth metacarpal bones, as shown in the x-ray in the vignette. Additionally, patients with pseudohypoparathyroidism type 1A have resistance to various other G-protein-coupled hormones, including TSH, LH, FSH, and GnRH. In contrast, those with paternally transmitted GNAS variants have the physical phenotype of Albright hereditary osteodystrophy but normal serum Ca, phosphate, and PTH concentrations. This is referred to as pseudopseudohypoparathyroidism (Answer E). DiGeorge syndrome (22q11.2 deletion syndrome) (Answer C) results from abnormal development of the third and fourth branchial pouches and is associated with parathyroid aplasia or hypoplasia, thymic aplasia or hypoplasia, cardiac abnormalities, developmental delay, and characteristic facial appearance.

34.4. Answer D) Pseudohypoparathyroidism Type 1A

In this setting, PTH would be low, not high. An activating variant in the gene encoding the calcium-sensing receptor (CASR) (Answer A) is the usual cause of autosomal dominant hypocalcemia and manifests with hypocalcemia and inappropriately "normal" PTH concentrations. The high PTH seen in this case would not be consistent with autosomal dominant hypocalcemia

Autoimmune polyglandular syndrome type 1 (Answer B) results in immunological destruction of the parathyroid glands and presents with hypoparathyroidism, primary adrenal insufficiency, and mucocutaneous candidiasis, none of which is present in this patient.

Educational Objective:

Diagnose pseudohypoparathyroidism type 1A

The End

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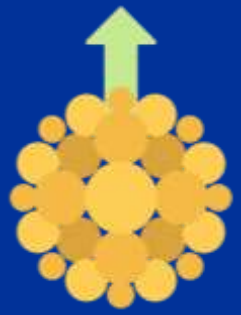
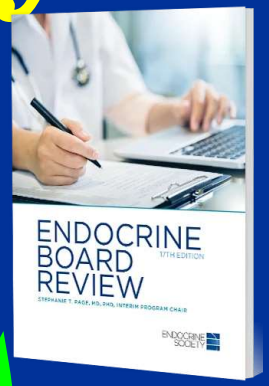
مراجعات البورد في الغدد

EBR.17

Lipids and Obesity

Lipids and Obesity





الدكتور محمد الشعباني

1.1. A 45-year-old ♂ presents for evaluation of cardiovascular disease risk. He has no chest pain or shortness of breath, and he does not smoke cigarettes. His father had a myocardial infarction at age 48.
Lipid profile: Total cholesterol: 240 mg/dL (<200). LDL: 150 mg/dL (<100). HDL: 40 mg/dL (>60). Tg: 180 mg/dL (<150). Exam: BMI 29. BP: 130/85. .
Results of diabetes screening and electrocardiography are normal.
Initiation of statin therapy is discussed, but the patient is hesitant because he has read about adverse effects, such as myopathy and increased diabetes risk. He recently fractured his ankle from a fall and is unable to exercise. Given this patient's moderate cardiovascular risk profile, which of the following is the best next step in management and why?

A. Determine coronary artery calcium score to refine cardiovascular risk and guide the decision on statin therapy.
B. Determine coronary artery calcium score to rule out coronary artery disease in the context of hyperlipidemia.
C. Initiate ezetimibe therapy to address his elevated LDL cholesterol
D. Reassure the patient and defer any further testing or treatment, as traditional risk factors are sufficient for assessment.

1.2. ANSWER: A) Determine coronary artery calcium score to refine cardiovascular risk and guide the decision on statin therapy: For adults at an intermediate 10-year risk (7.5%–20%) of atherosclerotic cardiovascular disease, for whom the benefit of statin therapy remains uncertain, the American College of Cardiology/American Heart Association guidelines for cholesterol management (2018) and primary prevention (2019) recommend determining a coronary artery calcium (CAC) score to help with risk stratification (Answer A). CAC scoring should not be used in patients at high risk, including those with familial hypercholesterolemia, since it can give a false-negative result. However, a CAC score of 100 or greater would provide evidence in favor of starting statin therapy. The CAC score is not a measure of coronary artery disease, so it cannot be used to rule out this condition (Answer B).

1.3. ANSWER: A) Determine coronary artery calcium score to refine cardiovascular risk and guide the decision on statin therapy: For adults Ezetimibe therapy alone (Answer C) does not provide the same cardioprotective properties as statins. Traditional risk factors alone may underestimate risk in younger individuals and asymptomatic patients who should be screened for coronary artery disease. Thus, simply reassuring the patient and deferring further testing or treatment (Answer D) is incorrect.

Educational Objective:

Describe the utility and indications for coronary calcium scoring in refining cardiovascular risk in the primary prevention of coronary artery disease.

2.1. A 52-year-old ♀ with cardiovascular disease risk. She has a 20-pack-year history of cigarette smoking (quit 5 years ago), hypertension that is adequately treated with lisinopril (20 mg daily), and hyperlipidemia. Man presents for evaluation. Lipid profile: LDL cholesterol 150 mg/dL (<100). HDL: 45 mg/dL (>60). Tg: 200 mg/dL (<150). She has no history of diabetes. Her father had a stroke at age 45. Her current Framingham risk score places her in the intermediate-risk category. Her primary care provider recommended atorvastatin 20 mg/day. Since starting this medication, she has had myalgias with exercise. Repeated lipid profile 6 months after starting atorvastatin: LDL: 110 mg/dL. HDL: 48 mg/dL. Tg: 140 mg/dL. Lipoprotein (a) 70 mg/dL (<30). Which medications should be initiated to address her elevated Lp(a) and lower her cardiovascular risk?

A. Aspirin
B. Ezetimibe
C. Fenofibrate
D. PCSK9 inhibitor

2.2. ANSWER: D) PCOSK9 inhibitor. Lipoprotein(a) (Lp(a) is a genetically determined lipid particle that has emerged as an important risk factor for cardiovascular diseases, particularly in individuals who may not have typical risk factors, such as high LDL cholesterol or Hypertension. Research has been increasingly focused on the clinical implications of Lp(a) in primary prevention, especially since it is not influenced by lifestyle factors such as diet, exercise, or cigarette smoking. However, some organizations suggest considering Lp(a) testing in individuals with a family history of premature cardiovascular disease, those with unexplained cardiovascular disease, or individuals at intermediate risk who have a normal lipid panel with the exception of elevated Lp(a). The 2024 updated NLA scientific statement advises testing all adults at least once in their lifetime and selective screening in high-risk youth.

2.3. ANSWER: D) PCOSK9 inhibitor.

PCSK9 inhibitors (Answer D) reduce Lp(a) levels. Other lipid-lowering therapies, such as ezetimibe (Answer B), do not alter Lp(a) levels.

Fenofibrate (Answer C) is incorrect because Lp(a) is associated with atherogenic particles related to LDL cholesterol, not triglycerides.

Aspirin (Answer A) does not lower Lp(a).

Educational Objective: Recommend adjustments in lipid management based on elevated lipoprotein(a) in primary prevention.

3.1. A 48-year-old ♀ with BMI 30. Presents with elevated triglycerides.

Lab: Tg: 450 mg/dL (<150). LDL: 150 mg/dL (<100).
HDL: 42 mg/dL (>60). Glucose: 108 mg/dL.

She consumes a diet high in sugar and refined carbohydrates and exercises inconsistently. She does not drink alcohol and has no history of pancreatitis. There is no family history of coronary artery disease. Which is the most appropriate initial management for her elevated triglycerides and prediabetes?

A. Bariatric surgery
B. Fibrate therapy
C. Metformin and lifestyle changes
D. Statin therapy

3.2. ANSWER: C) Metformin and lifestyle changes

This patient is overweight and has prediabetes and elevated triglycerides. She meets criteria for metabolic syndrome and would benefit from weight loss and exercise to prevent diabetes and lower her triglyceride levels. In patients without T2D, diet, exercise, and metformin therapy (Answer C) are initial considerations for lowering triglyceride levels. Metformin can lower triglyceride levels by approximately 10-20%, particularly in patients with elevated baseline triglycerides and insulin resistance. Statin therapy (Answer D) would lower LDL and triglyceride levels, but it would not treat prediabetes. Fibrate therapy (Answer B) is indicated if triglyceride levels are greater than 1000 mg/dL (>11.30 mmol/L). Bariatric surgery (Answer A) would not be the initial management of this patient with class I obesity.

Educational Objective:

Manage elevated triglyceride levels in patients with prediabetes.

4.1. A 30-year-old ♀ seeks advice on weight loss. She is a graduate student and has been writing her dissertation, which has considerably changed her lifestyle. She sits at her computer most of the day, gets little exercise, and has been craving junk food. She has gained 11 kg in the last year. BMI 30. She wants to lose weight but does not want to start medication. She would like to begin a diet, but she is unsure which one would have the best results. She asks about the evidence supporting various meal plans, including benefits of intermittent fasting (16 hours of fasting/24 hours). Intermittent fasting primarily aids weight loss through which of the following mechanisms?

A. Boosting metabolism by increasing calorie expenditure
B. Improving digestion efficiency
C. Improving sleep hygiene
D. Increasing muscle mass
E. Reducing overall caloric intake

4.2. ANSWER: E) Reducing overall caloric intake

Many diet regimens for weight loss exist, including versions of the low-carbohydrate diet, low glycemic-index diet, ketogenic diet, low-fat, high-fiber diet, and, more recently, intermittent fasting diet. Intermittent fasting refers to fasting for 12 hours or longer. Time-restricted feeding involves restricting food intake to certain timeframes, usually between 6 and 12 hours a day. The premise behind intermittent fasting is that caloric restriction on fasting days shifts fuel metabolism from carbohydrates and glucose (after glycogen stores are depleted) to lipolysis and the generation of ketone bodies. Intermittent fasting improves glucose and lipid metabolism, reduces inflammation, reduces liver fat, and reduces blood pressure. However, intermittent fasting has been shown to increase heart rate variability With reduced caloric intake (Answer E), intermittent fasting leads to 5- to 7-lb (2.3- to 3.2-kg) weight loss over 3 months, but it does not change muscle mass (Answer D). It reduces energy expenditure, not increases it (Answer A). Intermittent fasting does not affect digestive efficiency (Answer B) and does not necessarily result in improved sleep (Answer C).

Educational Objective: Explain the rationale for intermittent fasting diets and their efficacy for weight loss and improved health.

5.1. A 45-year-old ♀ with a family history of premature cardiovascular disease presents for lipid management. Heterozygous familial hypercholesterolemia was diagnosed after genetic testing revealed a pathogenic variant in the LDL receptor gene. Her current LDL-cholesterol is 220 mg/dL (5.70 mmol/L), despite a treatment regimen of Atorvastatin 80 mg/day, and Ezetimibe 10 mg/day.
Given her diagnosis of familial hypercholesterolemia, which of the following treatment options is most likely to further reduce LDL to target and improve cardiovascular outcomes?

A. Add bempedoic acid, 180 mg daily
B. Change atorvastatin to Inclisiran, 184 mg every 6 months
C. Change atorvastatin to rosuvastatin, 20 mg daily
D. Discontinue Atorvastatin and initiate Evolocumab, 140 mg injection once every 2 weeks

5.2. ANSWER: D) Discontinue atorvastatin and initiate evolocumab, 140 mg injection every 2 weeks

PCSK9 inhibitors, such as alirocumab and evolocumab (Answer D), are used to treat hypercholesterolemia, particularly in patients with familial hypercholesterolemia, when cholesterol levels remain high despite other treatments. The indications for PCSK9 inhibitors in the setting of familial hypercholesterolemia typically include:

Heterozygous familial hypercholesterolemia. When a patient has heterozygous familial hypercholesterolemia and is not reaching target LDL-cholesterol levels with maximal statin therapy (and possibly other lipid-lowering treatments, such as ezetimibe).

Homozygous familial hypercholesterolemia. For patients with homozygous familial hypercholesterolemia who have not responded adequately to other treatments, such as high-dose statins and other lipid-lowering agents.

5.3. ANSWER: D)

These patients often have very high LDL-cholesterol levels and may require aggressive treatments, such as PCSK9 inhibitors, to help control cholesterol.

These medications can significantly lower LDL cholesterol by inhibiting PCSK9, which is a protein that normally promotes the degradation of LDL receptors in the liver, leading to more LDL cholesterol being cleared from the bloodstream. This helps reduce LDL-cholesterol levels, especially in individuals with genetic conditions, such as familial hypercholesterolemia, in which cholesterol clearance is impaired.

Switching atorvastatin to rosuvastatin (Answer C) would not achieve the LDL-cholesterol target Bempedoic acid (Answer A) results in modest LDL-cholesterol reduction and would not be appropriate for this patient.

5.4. ANSWER: D)

Inclisiran (Answer B) is a small interfering RNA (siRNA) drug that lowers LDL cholesterol by inhibiting the production of PCSK9, a protein that increases LDL-receptor degradation. By reducing PCSK9 levels, Inclisiran increases LDL-receptor recycling and enhances LDL-cholesterol clearance from the bloodstream. Inclisiran is indicated for statin-intolerant patients and is not approved for familial hypercholesterolemia.

Educational Objective:

Recommend PCSK9 inhibitors in patients with heterozygous familial hypercholesterolemia.

6.1. A 52-year-old ♂ with class I obesity, metabolic syndrome, and prediabetes is referred for evaluation.

Lipid panel: Tg: 300 mg/dL (<150). HDL: 24 mg/dL (>60). LDL: 132 mg/dL (<100). He is prescribed a statin, which improves his lipid parameters, but his HDL remains < 30 mg/dL. He is scheduled to see a nutritionist for weight-loss counseling and wants to know if a specific change in his diet may improve his HDL levels.

Which dietary modifications could help increase his HDL levels?

A. Decrease intake of refined sugars and high glycemic index foods
B. Increase intake of β-carotene
C. Increase intake of distilled alcohol
D. Increase intake of high-potency multivitamins
E. Increase intake of monounsaturated and polyunsaturated fats (e.g., olive oil, nuts)

6.2. ANSWER: E) Increase intake of monounsaturated and polyunsaturated fats (e.g., olive oil, nuts): For individuals with low HDL-cholesterol levels, a targeted nutritional approach can be helpful in raising HDL and improving overall lipid profiles. While genetics plays a role in HDL-cholesterol levels, lifestyle and diet are also key contributors. Dietary recommendations to help boost HDL cholesterol include healthy fats (e.g., monounsaturated fats). Sources include olive oil, avocados, and nuts (especially almonds, walnuts, and pistachios) (Answer E). Omega-3 fatty acids found in fatty fish (e.g., salmon, mackerel, sardines), flaxseeds, chia seeds, and walnuts can also help raise HDL cholesterol and improve overall heart health. Patients should be advised to avoid industrially processed trans fats found in many baked goods, fried foods, and processed snacks, as these fats lower HDL cholesterol and raise LDL Cholesterol..

6.3. ANSWER: E) Increase intake of monounsaturated and polyunsaturated fats (e.g., olive oil, nuts):

While a moderate amount of saturated fat (e.g., from coconut oil or dark chocolate) can be part of a healthy diet, excessive consumption of red meat, butter, and full-fat dairy products can negatively affect HDL-cholesterol levels. -Carotene (Answer B) and multivitamins (Answer D) do not affect HDL-cholesterol levels.

Decreasing intake of refined sugars and high glycemic index foods (Answer A) would lower glucose and not address HDL-cholesterol levels. Increasing intake of distilled alcohol (Answer C) is dangerous and would not increase HDL-cholesterol levels.

Educational Objective:

Recommend the best nutritional management of low HDL cholesterol.

7.1. A 60-year-old ♀ with T2D, class II obesity (BMI:35), and hypertension presents with a recent diagnosis of metabolic-dysfunction-associated steatotic liver disease. Her ALT is mildly elevated at 50 U/L (0.84 µkat/L), and ultrasonography shows hepatic steatosis. Her Fibrosis 4 index is 1.5. She is offered a liver biopsy but declines. She is currently on metformin and semaglutide for diabetes; lisinopril for hypertension; and atorvastatin, 20 mg daily, for hyperlipidemia. With dietary modification following a Mediterranean meal plan and a structured exercise program, she loses 10% of her total body weight in 6 months and feels more energetic. However, despite weight loss, her ALT concentration remains elevated at 50 U/L (0.84 µkat/L).

Which is the most appropriate management strategy for this patient?

A. Initiate more aggressive weight-loss therapy with Tirzepatide 2.5 mg/week
B. Prescribe Pioglitazone 30 mg/day, to reduce hepatic inflammation
C. Recommend a vegan diet to induce weight loss and improve glycemic control
D. Refer to hepatology to rule out other causes of advanced liver disease
E. Start icosapent ethyl for liver protection and cardiovascular risk reduction

7.2. ANSWER: D) Refer to hepatology to rule out other causes of advanced liver disease: This patient has T2D and metabolic-dysfunction-associated steatotic liver disease based on ultrasonography but has a Fibrosis-4 index below 1.3, indicating that fibrosis is unlikely. Although weight loss is indicated for hepatic steatosis and should improve liver transaminase levels, her ALT concentration remains high, indicating possible other causes of chronic liver disease. Thus, a referral to hepatology (Answer D) is necessary. Tirzepatide (Answer A) is superior to semaglutide for glycemic control and weight loss, but at a low dosage of 2.5 mg weekly, it would not stimulate greater weight loss. Pioglitazone (Answer B) would not treat nonmetabolic causes of chronic liver disease. Icosapent ethyl (Answer E) has not been shown to have benefits for metabolic-dysfunction-associated steatotic liver disease A vegan diet (Answer C) would result in weight loss and improve hepatic steatosis, but it would not rule out other causes of advanced liver disease.

Educational Objective: Manage metabolic-dysfunction-associated steatotic liver disease in patients with diabetes.

8.1. A 45-years-old ♂ with 35-year history of T1D is treated with intensive insulin therapy via an insulin pump. He has developed weight gain over the past 10 years resulting in class III obesity (BMI 47), metabolic syndrome, and obstructive sleep apnea requiring continuous positive airway pressure. His inulin requirements have nearly doubled in the past 10 years. He has hypertension requiring two antihypertensive agents and elevated cholesterol treated with Rosuvastatin He has been to a nutritionist, and despite counseling about lifestyle modification, he has been unable to lose > 4.5 kg, which he regained over time. He has not been able to tolerate anti-obesity agents, such as phentermine, topiramate, naltrexone, and bupropion, due to adverse effects. A trial of Semaglutide titrated from 0.5 mg/week to 2 mg/week results in a modest weight loss of 11 kg, but his weight has plateaued (current BMI 36), and he is seeking more effective weight-loss strategies. He agrees to consider bariatric surgery. Which best describes the expected effects of Roux-en-Y gastric bypass on his glycemic control?

A. Complete cessation of rapid-acting prandial insulin
B. Decreased insulin sensitivity and higher basal insulin requirements
C. Increased insulin sensitivity and improved glycemic control in the short term and increased risk of hypoglycemia
D. Reduced glucose variability

8.2. Answer C) Increased insulin 8 sensitivity and improved glycemic control in the short term and increased risk of hypoglycemia: Weight gain in patients with T1D is associated with several factors related to lifestyle factors and insulin use and can result in double diabetes with the presence of metabolic syndrome and adiposity-related chronic disease. Although lifestyle and behavior modification are needed, often these do not lead to sustained weight loss. Antiobesity pharmacotherapy, including phentermine, GLP-1 receptor agonists, and other agents, may elicit modest weight loss, but this patient has class II obesity with several comorbidities. He meets National Institutes of Health criteria for bariatric surgery, and gastric bypass would be expected to induce 25-30% total body weight loss and improve metabolic syndrome and obstructive sleep apnea. However, in patients with T1D, a greater risk of hypoglycemia is noted with altered nutrient transit, and this requires reduced prandial and basal insulin doses. (Thus, Answer C is correct and Answer B is incorrect). A greater risk of diabetic ketoacidosis and infection are also noted in patients with T1D. Cessation of rapid-acting prandial insulin (Answer A) would not be possible in the setting of T1D, and this may result in high glucose variability and possible DKA. Gastric bypass is associated with increased, not decreased, glucose variability (Answer D). Therefore, sleeve gastrectomy is the preferred procedure in these patients.
Educational Objective: Describe anticipated outcomes of bariatric surgery in patients with obesity and T1D.

9.1. A 38-year-old ♀ is referred for weight loss. She has features of metabolic syndrome, including impaired fasting glucose and dyslipidemia. Height 168 cm, weight 81 kg. BMI: 29. She has had slow, steady weight gain since puberty. Menarche was 13 years old, and she has always had normal menstrual cycles. She has never been pregnant. She has a strong family history of obesity. Her mother underwent gastric bypass at age 52 and lost approximately 27 kg. Her father was recently diagnosed with steatohepatitis and Both her brothers are obese. She currently takes metformin but no other medications. Physical examination findings are notable for generalized adiposity but are otherwise normal.

A predisposing pathogenic variant in which of the following genes is most likely to be present in this family?

A. FTO (fat mass and obesity associated)
B. LEP (leptin)
C. LEPR (leptin receptor)
D. MC4R (melanocortin 4 receptor)

9.2. ANSWER: A) FTO (fat mass and obesity associated)

While lifestyle and environmental factors are extremely important in weight gain, genetic factors are also important. Genome-wide association studies have identified a number of loci that are determinants of BMI. The single gene most commonly associated with typical human obesity is FTO (Answer A). This association has been documented in several different populations. Individuals with the at-risk allele weigh 2-3 kg more than those without the allele. Many studies have tried to determine the mechanisms by which the at-risk alleles in the FTO gene produce increased BMI. Most of the physiological data suggest this occurs through a predisposition for increased food intake. However, a recent study using the most definitive methods applied to date provides strong evidence that DNA near the FTO gene interacts with other genes at a distance to foster the development of adipocyte precursors to either white or brown/beige adipocytes Pathogenic variants in the genes encoding the melanocortin 4 receptor (MC4R), leptin (LEP), and the leptin receptor (LEPR) (Answers B, C, and D) have been found in humans and are associated with obesity. However, these pathogenic variants are uncommon (MC4R) or rare (LEP and LEPR), typically involve consanguinity, and are associated with extreme obesity that develops in childhood. This is not the phenotype of the patient described in this vignette.

Educational Objective: Identify the common gene variants that predispose to obesity.

10.1. A 19-year-old ♀ accompanied by her parents seeks help managing severe obesity that began in the first year of life. Her growth rate was faster than that of other children her age, and she always appeared to have "big bones." She underwent normal puberty. Her school performance has been normal, although she struggles with depression. current BMI 48. Which genetic syndromes of obesity does she most likely have?

A. Leptin deficiency
B. Leptin receptor deficiency
C. Melanocortin 4 receptor (MC4R) pathogenic variant
D. Prader-Willi syndrome

10.2. ANSWER: C) Melanocortin 4 receptor (MC4R) pathogenic variant

Although knowledge of the monogenic forms of severe childhood obesity is most relevant for pediatric endocrinologists, adult endocrinologists will occasionally encounter a patient with one of these syndromes, and genetic forms of obesity provide insights into important pathways that regulate body weight. The most common monogenic form of early-onset obesity involves pathogenic variants in the gene that encodes the melanocortin 4 receptor (MC4R) (Answer C). MC4R pathogenic variants are thought to occur in as many as 1 in 1000 individuals. The melanocortin 4 receptor is involved in hypothalamic signaling along the neural pathway that responds to leptin. Individuals who have pathogenic variants in the genes encoding leptin (Answer A) or the Leptin receptor (Answer B) individuals have hypothalamic hypogonadism and subtle impairments in GH and immune function.

10.3. ANSWER: C) Melanocortin 4 receptor (MC4R) pathogenic variant

In contrast, individuals with MC4R pathogenic variants present with severe obesity but normal reproductive function. They also have normal growth and "big bones" that are thought to be due to increased insulin levels during development. Prader-Willi syndrome (Answer D) is a multisystem disorder caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13. Typical features of Prader-Willi syndrome include hypotonia, poor feeding after birth, learning disabilities, growth retardation, behavioral problems, hypothalamic hypogonadism, and cryptorchidism. The initial screening genetic test, DNA methylation analysis, is important in making a definitive diagnosis.

Educational Objective: Differentiate among the common monogenic forms of severe childhood obesity.

11.1. A 23-year-old ♂ seeks help addressing high cholesterol. He was seen at a local health fair where he was told that his cholesterol was extremely high and that he should seek care. He also mentions a rash on his legs.

Exam: has small yellowish papules on his abdomen, lower back, extensor surfaces of his arms, and thighs (see image).

Fasting lipid panel: Total cholesterol: 325 mg/dL (<200). Tg: 3450 mg/dL (<150). HDL: 30 mg/dL (>60). LDL: cannot be calculated. Which abnormalities does this patient most likely have?

A. Apolipoprotein E2/E2
B. ATP-binding cassette A1 (ABCA1) deficiency
C. LDL receptor deficiency
D. Lipoprotein lipase deficiency
E. Overproduction of apolipoprotein B

11.2. ANSWER: D) Lipoprotein lipase deficiency

This patient has marked hypertriglyceridemia. Lipoprotein lipase (LPL) is the enzyme responsible for the catabolism of triglyceride-rich lipoprotein particles. Deficiency of LPL (Answer D) will therefore produce the phenotype observed in this patient. Deficiency of LPL's cofactor, apolipoprotein C2, can also produce this clinical picture. Individuals with severe hypertriglyceridemia develop eruptive xanthomas, which are the skin lesions described in this patient The phenotype associated with apolipoprotein E2/E2 (Answer A) is present in patients with dysbetalipoproteinemia, which is also referred to as type III hyperlipidemia, or broad-beta disease. Classic skin manifestations include tuberoeruptive lesions on the elbows and palmar xanthomas.

11.3. ANSWER: D) Lipoprotein lipase deficiency

The apolipoprotein E2/E2 phenotype occurs in approximately 1 in 100 persons, but the development of characteristic dyslipidemia is infrequent and usually appears later in life due to acquired medical conditions such as hypothyroidism, obesity, diabetes, or estrogen replacement therapy. ATP-binding cassette A1 (ABCA1) is a protein involved in moving cholesterol from peripheral tissues onto HDL particles. Deficiency of this protein (Answer B) results in the condition known as Tangier disease, characterized by very low HDL-cholesterol levels and the classic physical examination finding orange tonsils, which this patient does not have LDL-receptor deficiency (Answer C) results in the condition known as familial hypercholesterolemia. Patients with familial hypercholesterolemia have very high LDL-cholesterol levels, tendinous xanthomas, and premature coronary artery disease..

11.4. ANSWER: D) Lipoprotein lipase deficiency

Overproduction of apolipoprotein B (Answer E) is the underlying problem in patients with familial combined hyperlipidemia. These individuals can have modest elevations in either triglycerides, LDL cholesterol, or both. This condition is associated with atherosclerotic cardiovascular disease; however, the degree of triglyceride elevation seen in this condition is not as high as it is in this patient, and it is not associated with eruptive xanthomas.

Educational Objective:

Identify the clinical features of genetic hyperlipidemias.

12.1. An 18-year-old ♂ is referred for abnormal cholesterol levels. The patient describes progressive fatigue over the last 4 years. When his parents noticed clouding of his corneas, they took him to see an ophthalmologist who ordered laboratory tests.

Lipid (fasting): HDL: 6 mg/dL (>60). LDL: 190 mg/dL (<100). Tg: 290 mg/dL (<150).

Exam: he is a thin, ill-appearing young man. His tonsils are normal color and size, and he has no tendinous xanthomas. Additional lab testing documents 3+ proteinuria and Cr 2.8 mg/dL.

Which abnormalities does this patient most likely have?

A. ATP-binding cassette A1 (ABCA1) deficiency
B. Defective apolipoprotein B
C. Lecithin-cholesterol acyltransferase deficiency
D. Lipoprotein lipase deficiency
E. Surreptitious testosterone use

12.2. ANSWER: C) Lecithin-cholesterol digesting cholesterol

The most striking feature of this patient's clinical presentation is his very low HDL-cholesterol level. His phenotype is typical of lecithin-cholesterol acyltransferase (LCAT) deficiency (Answer C). The LCAT enzyme is responsible for converting the relatively polar free cholesterol in the developing HDL particle into nonpolar cholesterol esters. Cholesterol esters are then "trapped" in the HDL particle to be taken back to the liver. When LCAT is deficient, free cholesterol does not stay associated with the HDL particle, resulting in low circulating HDL-cholesterol levels. This condition is associated with cholesterol accumulation in the eyes, which causes corneal clouding. Affected patients also have proteinuria that develops in childhood, progressive kidney dysfunction leading eventually to end-stage kidney disease, and anemia due to red blood cell fragility secondary to abnormal membrane lipids ATP-binding cassette A1 (ABCA1) deficiency (Answer A), or Tangier disease, can also cause very low HDL-cholesterol levels, but it is not associated with abnormal kidney function.

12.3. ANSWER: C) Lecithin-cholesterol digesting cholesterol

Tangier disease is associated with cholesterol accumulation in lymphoid tissue that results in orange tonsils, a classic physical finding. Surreptitious testosterone use (Answer E) can lower HDL levels, sometimes dramatically. However, individuals abusing purrs testosterone would be expected to exhibit findings of excess androgens (increased muscle mass, acne) that are not described here, and such individuals would not have the eye or kidney problems described in this patient. Defective apolipoprotein B (Answer B) has a phenotype similar to that of familial hypercholesterolemia, with tendinous xanthomas and very high LDL levels. Lipoprotein lipase deficiency (Answer D) results in very high triglyceride levels (>1000 mg/dL (>11.30 mmol/L)) and a more modest decrease in HDL.

Educational Objective: Describe the clinical features of conditions that cause very low HDL-cholesterol.

13.1. A 23-year-old Japanese ♀ seeks consultation after a high cholesterol level was documented during screening at a health fair. She is healthy, takes an oral contraceptive and no other medications, and drinks 1-3 alcoholic beverages/week. Lipid (fasting): Total cholesterol: 230 mg/dL (<200). HDL: 110 mg/dL (>60). Tg: 78 mg/dL (<150). LDL: 120 mg/dL (<100). Which is the most likely explanation for this patient's lipid levels?

A. Apolipoprotein A1 deficiency
B. Cholesteryl ester transfer protein deficiency
C. Interference with lipid assays
D. Lipoprotein lipase deficiency
E. Oral contraceptive use

13.2. ANSWER: B) Cholesteryl ester transfer protein deficiency

This presentation is classic for cholesterol ester transfer protein (CETP) deficiency (Answer B). CETP catalyzes the exchange of triglyceride and cholesterol ester between triglyceride-rich lipoprotein particles and HDL particles. In normal individuals, the result is a net transfer of triglyceride to HDL, which leads to increased catabolism and reduced HDL-cholesterol concentrations. Persons with CETP deficiency have very high HDL cholesterol. This condition is more common in individuals of Asian ancestry. On the basis of this underlying physiology, pharmaceutical companies have developed a number of CETP inhibitors. Surprisingly, these medications to date have not been shown to reduce cardiovascular disease risk despite dramatically raising HDL-cholesterol concentrations.

13.3. ANSWER: B) Cholesteryl ester transfer protein deficiency

Oral contraceptives (Answer E) can raise HDL-cholesterol levels but typically not to this degree. Their use is often associated with increased triglycerides

Several medical conditions, including multiple myeloma and other paraproteinemias, can cause problems with the laboratory measurement of HDL cholesterol (Answer C), but in these cases, HDL cholesterol is low, not high.

Apolipoprotein Al deficiency (Answer A) and lipoprotein lipase deficiency (Answer D) are associated with low, not high, HDL cholesterol.

Educational Objective:

Describe the function of the cholesteryl ester transfer protein and the clinical features of cholesteryl ester transfer protein deficiency.

14.1. A 22-year-old ♀ with class III obesity complicated by obstructive sleep apnea, impaired glucose tolerance, and PCOS underwent gastric bypass surgery 9 months ago. She can tolerate small low-carbohydrate meals and has lost > 23 kg. Current BMI 36, down from 45 before surgery. Her menses are now regular, and she and her husband are interested in pregnancy. She is adherent to her regimen of daily replacement supplements, including a prepregnancy vitamin, folic acid, sublingual vitamin B12, calcium citrate, vitamin D3, and iron daily. Which is the most appropriate clinical advice for this patient regarding pregnancy planning?

A. Avoid pregnancy (with use of an intrauterine device) until she is weight stable.
B. Avoid pregnancy (with use of an oral contraceptive pill) until she is weight stable
C. Proceed with pregnancy as long as HbA1c is in the normal range (i.e., <5.7% (<39 mmol/mol))
D. Proceed with pregnancy as long as she increases vitamin supplementation dosages to those recommended during pregnancy
E. Proceed with pregnancy but advise her that breastfeeding after gastric bypass is contraindicated

14.2. ANSWER: A) Avoid pregnancy (with use of an intrauterine device) until she is weight stable

More than 80% of bariatric procedures are performed in women, and approximately half of these procedures are performed in reproductive-aged women. Thus, it has become increasingly common for women who have undergone bariatric surgery to present for preconception counseling or prenatal care. A joint 2013 clinical practice guideline by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery recommends that women avoid conception for 12-18 months after bariatric surgery because this time frame is when women are actively losing the most weight. This delay is done in an effort to optimize weight loss and reduce the potentially adverse effect of postbariatric surgical nutritional deficiencies.

14.3. ANSWER: A) Procedures that create malabsorption, such as biliopancreatic diversion, jejunoileal bypass, or Roux-en-Y bypass, may interfere with the absorption of oral contraceptives (Answer B), thereby reducing their effectiveness. Thus, an Intrauterine device (Answer A) is a preferred method of contraception.

As discussed, pregnancy during the time of active weight loss after bariatric surgery is not recommended (therefore, Answers C, D, and E are incorrect). Breastfeeding is not contraindicated following bariatric surgery. Monitoring nutritional status (i.e., prealbumin levels) and micronutrient levels (especially iron, ferritin, vitamin B12, calcium, PTH, 25-hydroxyvitamin D) is essential after gastric bypass, as well as before, during, and after pregnancy.

Educational Objective: Provide pregnancy counseling to women who have undergone bariatric surgery.

15.1. A 37-year-old ♂ seeks evaluation for 15 years. A cholesterol panel was done 1 year ago, and a repeat panel was done last week. He is concerned about the increase in his cholesterol. Since his lipid panel 1 year ago, he has gained 3 kg. BMI 28. He reports working longer hours (sedentary desk job), sleeping less, and feeling quite fatigued. He has changed his diet and eliminated fried foods and sweets but struggles with constipation. He drinks 2 glasses of red wine/day. He has been exercising regularly to lose weight. His wife states that he has been snoring a lot lately. He has a family history of T2D, but HbA1c last year was 5.2% (33 mmol/mol). Which is the most likely cause of this patient's increased cholesterol?

A. Alcohol intake
B. Hypothyroidism
C. Sleep apnea
D. Undiagnosed diabetes

Measurement	Last year	Current
Total cholesterol	190 mg/dL	220 mg/dL
Triglycerides	115 mg/dL	130 mg/dL
LDL	123 mg/dL	150 mg/dL
HDL	43 mg/dL	44 mg/dL

15.2. ANSWER: B) Hypothyroidism

When caring for a patient with hyperlipidemia, the clinician must consider and rule out secondary causes. This patient had relatively normal lipid levels one year ago and now has elevated total and LDL without much change in triglycerides or HDL. The change over the last year suggests that the lipid abnormalities are not entirely genetic but due to something that has changed during this period. The changes described in the vignette are typical of those seen with hypothyroidism (Answer B). LDL and total cholesterol levels increase as hypothyroidism worsens and are increased by 30% in frank hypothyroidism. Both subclinical hypothyroidism and overt hypothyroidism are associated with an increased risk for cardiovascular disease. Sleep apnea (Answer C) per se does not alter lipid levels unless it is a manifestation of another condition such as insulin resistance and T2D. Undiagnosed diabetes (Answer D) would typically be expected to significantly increase triglyceride levels and reduce HDL levels without much change in LDL. This is not the case in this vignette. Alcohol intake (Answer A) is associated with increased triglycerides and has no effect on LDL concentrations.

Educational Objective: Identify hypothyroidism as a secondary cause of lipid abnormalities.

16.1. A 45-year-old ♀ seeks help losing weight. She has a seizure disorder, which has been treated with increasing dosages of gabapentin over the past 2 years. Her current dosage is 600 mg 3 times/day. Since starting this medication, she has gained 14 kg, Current BMI: 39. She has depression treated with Fluoxetine 20 mg/day. HbA1c 6.2% (44 mmol/mol), but she is not being treated for diabetes. Which weight-management strategies would most likely produce and sustain weight loss over the next 12 months in this patient?

A. Change from fluoxetine to mirtazapine
B. Change from fluoxetine to paroxetine
C. Change from gabapentin to topiramate
D. Initiate treatment with orlistat

16.2. ANSWER: C) Change from gabapentin to topiramate

Drug-induced weight gain is a common clinical problem. Several drug classes can cause weight gain, including antidiabetic medications, antipsychotic agents, antidepressant agents, mood stabilizers, glucocorticoids, and progestational agents. Several management options are available for patients who have drug-induced weight gain. One strategy is to reduce the dosage of the offending medication or to reconsider the value of that medication and to potentially stop it. Alternatively, a behavioral weight-management program can be instituted. Finally, the problematic medication can be stopped and an alternative Medication can be prescribed. For example, a GLP-1 receptor agonist or an SGLT-2 inhibitor can be used in place of, or in addition to, a sulfonylurea.

16.3. ANSWER: C) Change from gabapentin to topiramate

Among available antidepressant medications, fluoxetine is weight-neutral, and paroxetine and mirtazapine are associated with weight gain (thus, Answers A and B are incorrect). Topiramate (Answer C) is FDA-approved for epilepsy and migraine headaches. Although there are several studies in which it was used specifically for weight loss, it is not FDA-approved for weight loss. However, there is strong evidence that it produces a 6% to 8% weight loss that is sustained at 1 year. While both bupropion and topiramate can produce weight loss, topiramate produces more weight loss on average. Several clinical trials have examined the efficacy of orlistat (Answer E), and these studies show that although weight loss over the initial 6 months may exceed that seen with other diet types, weight loss at 1 year is no different from that seen with other hypocaloric diets.

Educational Objective:

Identify medications used for other conditions that can promote weight gain and suggest alternatives that are weight neutral or produce weight loss.

17.1. A 36-year-old ♀ with a peak lifetime BMI of 46 kg/m² had a laparoscopic gastric bypass operation in another state 8 weeks ago. She initially did well, but over the last 3 weeks she has had episodes of vomiting. In the last week, she has been vomiting almost everything she eats. Over the last 2 days, her husband says that she has become increasingly confused, dysarthric, and unsteady on her feet. Neurologic exam: confused and has nystagmus. She is unsteady while standing, has decreased sensation in her lower extremities, and has right third nerve palsy. This patient most likely has a deficiency of which of the following?

A. Folate
B. Niacin
C. Thiamine
D. Vitamin B12
E. Zinc

17.2. ANSWER: C) Thiamine

The symptoms displayed by this patient are characteristic of Wernicke encephalopathy, which is caused by thiamine deficiency (Answer C). Thiamine deficiency causes neuronal death due to metabolic dysfunction of astrocytes within the central nervous system. The classic triad of this condition is confusion, ataxia, and nystagmus. A wide range of other abnormalities can be seen, including cranial nerve dysfunction, peripheral neuropathies, seizures, and psychosis. Because thiamine is a water-soluble vitamin, body stores can be depleted within days to weeks of inadequate intake. The condition typically presents 4 to 12 weeks after bariatric surgery but can occur as early as 2 weeks and as late as 18 months. Although Wernicke encephalopathy is most often reported after gastric bypass surgery, it can occur after any type of bariatric surgery.

17.3. ANSWER: C) Thiamine: The most common antecedent is persistent vomiting, which then severely limits thiamine intake Other less common precipitating factors are intravenous glucose or parenteral nutrition administration without thiamine supplementation. The condition is important to recognize, as treatment with parenteral thiamine (100 mg daily for 7 to 14 days, or 500 mg 3 times daily for 3 days) must be administered to prevent serious morbidity. Although vitamin B_{12} deficiency (Answer D) can cause neurologic symptoms and signs, body stores of B_{12} are sizable, so deficiency does not usually occur until 6 to 24 months after bariatric surgery. Folate deficiency (Answer A) is uncommon and typically presents as anemia. Zinc deficiency (Answer E) is rare. It is associated with skin and hair findings and primarily occurs after biliary pancreatic diversion.

Educational Objective: Differentiate among vitamin deficiencies that can occur after gastric bypass surgery.

18.1. A 44-year-old ♂ recently presented with new-onset angina and a positive exercise stress test. He reports no history of hypertension, diabetes, or cigarette smoking. He follows no specific diet and exercises regularly. His father died of a myocardial infarction at age 45, and his brother underwent a revascularization procedure at age 46. His father and brother had lipid abnormalities characterized by high triglycerides and low HDL cholesterol. The patient's physical examination findings are normal.
Lipid profile (fasting): Total cholesterol: 270 mg/dL (<200). Tg: 300 mg/dL (<150). HDL: 30 mg/dL (>60). LDL: 180 mg/dL (<100). Which best explains his lipid profile?

A. Apolipoprotein A1 deficiency
B. Familial combined hyperlipidemia
C. Familial defective apolipoprotein B
D. Familial hypercholesterolemia
E. Lipoprotein lipase deficiency])

18.2. ANSWER: B) Familial combined hyperlipidemia

This vignette is typical of a person from a family with familial combined hyperlipidemia (Answer B), the most common lipid abnormality among patients with coronary artery disease. Familial combined hyperlipidemia was discovered from studies of families that had many individuals afflicted with coronary artery disease and high serum lipid concentrations. In a large percentage of patients, it is also associated with insulin resistance and metabolic syndrome. Although familial, the phenotype is typically not expressed until the third or later decades of life. Affected family members can have 1 of 3 lipid abnormalities:
hypercholesterolemia, hypertriglyceridemia, or both. The lipid abnormality may change and vary over time in affected individuals, probably because of nutritional factors (weight gain/weight loss).

18.3. ANSWER: B) Familial combined hyperlipidemia

Familial combined hyperlipidemia is caused by an overproduction of apolipoprotein B by the liver. The variable serum lipid phenotype reflects individual differences in the metabolism of VLDL depending on diet composition and other genes present in a particular person

Individuals with lipoprotein lipase deficiency (Answer E) have very high triglyceride levels, often greater than 1000 mg/dL (>11.30 mmol/L).

Familial hypercholesterolemia (Answer D) and familial defective apolipoprotein B (Answer C) are characterized by very high LDL-cholesterol levels (200-300 mg/dL (5.18-7.77 mmol/L)) and specific physical features, including tendinous xanthomas. Apolipoprotein A1 is the structural lipoprotein associated with HDL. Patients with apolipoprotein A1 deficiency (Answer A), also known as hypoalphalipoproteinemia, have very low HDL-cholesterol concentrations (<20 mg/dL [<0.52 mmol/L]).

Educational Objective: List the features of familial combined hyperlipidemia.

19.1. A 27-year-old ♂ is referred because of low blood cholesterol levels. He has had chronic abdominal symptoms, including bloating and diarrhea, and neurological symptoms, including spastic tremors. His red blood cell count indicates acanthocytosis.
Lipid profile (fasting): Total cholesterol: 56 mg/dL (<200). HDL: 24 mg/dL (>60). LDL: 24 mg/dL (<100). Tg: 38 mg/dL (<150). BMI 24. He has no abnormalities on physical examination.
He is advised regarding lifestyle modifications.
Which is one possible complication from this patient's condition?

A. Coronary artery disease
B. Kidney failure
C. Metabolic dysfunction-associated steatotic liver disease
D. Myositis
E. Tonsillitis

19.2. ANSWER: C) Metabolic dysfunction-associated steatotic liver disease

This patient has hypobetalipoproteinemia with reduced production of both LDL and VLDL (triglyceride). This condition is most often due to a defect in the liver production of apolipoprotein B—containing lipoproteins—because of defective production of apolipoprotein B or microsomal triglyceride transfer protein. With apolipoprotein B, a defective protein is associated with lower than one-half normal LDL levels. This condition should be distinguished from abetalipoproteinemia, in which LDL is markedly lower and affected patients develop deficiencies in fat-soluble vitamins. The third cause of this syndrome is a defect in angiopoietin-like protein 3 production. In hypobetalipoproteinemia, the inability to efficiently secrete lipoproteins from the liver can lead to metabolic dysfunction-associated steatotic liver disease (Answer C). This is also the adverse effect of drugs that inhibit microsomal triglyceride transfer protein or antisense therapies to reduce apolipoprotein B secretion. The patient should be instructed in lifestyle approaches to prevent liver disease, such as maintaining normal body weight and avoiding alcohol. Coronary artery disease (Answer A), kidney failure (Answer B), myositis (Answer D), and tonsillitis (Answer E) are not associated with low LDL.

Educational Objective: Identify metabolic dysfunction-associated steatotic liver disease as a complication of hypobetalipoproteinemia.

20.1. A 36-year-old ♀ with BMI 36 would like to lose 9 kg before her upcoming wedding. She is otherwise healthy and takes no medications. She exercises regularly. She does not want to take weight-loss medications but agrees to try a very low-calorie diet. When she returns for a follow-up in 3 months, she has lost 8 kg or 10% of her body weight BMI: 32.5. She is pleased, but she is struggling to maintain her weight because of constant hunger.

This patient's degree of weight loss is expected to result from which of the following changes in gut hormones that regulate appetite are expected?

Answer	Ghrelin	GLP-1	Peptide YY	Cholecystokinin
A	↑	↑	↓	↓
B	↓	↓	↓	↓
C	↑	↓	↓	↓
D	↑	↓	↑	↑

20.2. ANSWER: C) Ghrelin 1, peptide Y, cholecystokinin

Multiple peptide hormones secreted by the gastrointestinal tract regulate appetite through signaling primarily in the arcuate nucleus of the hypothalamus. Ghrelin is a peptide hormone secreted by cells lining the stomach, and it acts in the hypothalamus to stimulate hunger. Ghrelin production is suppressed after eating and rises again several hours later in the fasting state to stimulate hunger and food intake GLP-1, peptide YY, and cholecystokinin are peptide hormones secreted by the intestines in response to the presence of nutrients after food ingestion. They stimulate satiety pathways in the central nervous system and induce meal cessation. After a weight loss of approximately 10%, this hormonal profile shifts to favor weight regain. Ghrelin levels increase, and GLP-1, peptide YY, and cholecystokinin are suppressed (Answer C), causing the individual to feel hungrier and less satisfied after food intake. This pattern promotes weight regain and correlates with the experience that weight maintenance or continued weight loss becomes progressively more difficult after initial weight loss.

Educational Objective:

Identify the changes in gut hormones that occur after 10% weight loss.

21.1. A 42-year-old ♀ with PCOS is referred for weight management. PCOS was diagnosed at the age of 15 years. She gained weight through college and during her first job, which was very sedentary. She had a baby at age 36 years with the assistance of clomiphene but had difficulty losing weight after delivery. She has lost 8.kg over the last 6 months by participating in She's following a commercial weight-loss program and exercising regularly, but her weight has plateaued. She has a history of migraines, prediabetes, steatotic liver disease, and depression. Current medications include Metformin and a selective serotonin reuptake inhibitor. She also has gallstones, which were noted on abdominal ultrasonography 6 months ago. BMI 38. Which should be recommended for continued weight loss?

A. Liraglutide 3 mg daily
B. Naltrexone/bupropion
C. Orlistat
D. Phentermine/topiramate

21.2. ANSWER: D) Phentermine/SERD

Selection of weight-loss medications should be based on a patient's individual characteristics and clinical profile. Polycystic ovary syndrome is associated with overweight and obesity and significant metabolic dysfunction, including insulin resistance, type 2 diabetes, metabolic syndrome, and steatotic liver disease. Weight loss will improve this patient's metabolic and reproductive dysfunction. There are no data to suggest one This medication works better than another for weight loss in patients with polycystic ovary syndrome specifically. However, her clinical picture should guide the selection of a weight-loss medication, particularly her history of migraines and gallbladder disease.

Phentermine/topiramate (Answer D) is a combination medication containing phentermine (increasing dosages up to 15 mg daily) and topiramate (increasing dosages up to 92 mg daily).

21.3. ANSWER: D) Phentermine/SERD

Topiramate is approved by the US FDA for use in patients with chronic migraines to reduce the frequency of migraines and for patients with seizure disorders to reduce the frequency of seizures. Topiramate itself is not approved for weight loss. Given this patient's chronic migraines, phentermine/topiramate is a good choice for her.

One of the most common adverse effects of naltrexone/bupropion (Answer B) is headache, which would make it a poor choice in a patient with chronic migraines. Liraglutide, 3.0 mg daily (Answer A) is associated with gallbladder disease, including cholecystitis and gallstone pancreatitis. Over 3 years, treatment with liraglutide, 3.0 mg daily, for weight loss was associated with gallbladder disease in 4.9% of patients with a consistent risk of gallbladder problems throughout the 3-year observation period.

21.4. ANSWER: D) Phentermine/SERD

Given this patient's recurrent abdominal pain and known gallstones, liraglutide is not a good choice for her, although it would most likely improve her insulin resistance. Weight loss itself is associated with increased gallbladder dysfunction, believed to be due to decreased gallbladder contractility, and GLP-1 receptor agonists are associated with an added risk of gallbladder disease irrespective of the degree of weight loss.

Orlistat (Answer C) is typically not associated with substantial weight loss and is associated with significant gastrointestinal adverse effects.

Educational Objective:

Select appropriate medical therapy for weight loss based on a patient's individual characteristics and risk profile

22.1. A 51-year-old ♂ with an 8-year history of T2D is considering bariatric surgery with vertical sleeve gastrectomy. His current treatment regimen consists of metformin, Glipizide, and Sitagliptin. HbA1c: 9.2% (77 mmol/mol). He has been resistant to starting insulin because he fears further weight gain. He has heard that although bariatric surgery can result in diabetes remission, the remission may be short-lived. In counseling this patient, it would be most accurate to explain that in recent clinical trials, the rate of diabetes remission (defined as HbA1c <6.5% [<48 mmol/mol] on no glucose-lowering medications) 5 years after sleeve gastrectomy is approximately which of the following?

A. 0%
B. 10%
C. 20%
D. 50%
E. 75%

22.2. ANSWER: C) 20% Over the last 5 years, an increasing body

A wealth of data has emerged on the benefits of bariatric surgery on glycemic control in patients with type 2 diabetes. Early studies were simply case series—not randomized controlled trials—that suggested high rates of remission. However, these studies did not always define remission rigorously. The

STAMPEDE trial (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) is one of the first prospective randomized controlled trials to compare traditional medical therapy for type 2 diabetes with either gastric bypass surgery or sleeve gastrectomy. The patients enrolled had a BMI of 27 to 43 kg/m^2 at baseline complicated by type 2 diabetes. These investigators defined remission a priori as a hemoglobin A level less than 6.0% (<42 mmol/mol) on no glucose-lowering medications.

22.3. ANSWER: C) 20% Over the last 5 years, an increasing body

Five-year follow-up data on 134 of the 150 participants with type 2 diabetes in the original cohort showed that 14 patients who 29% of patients who underwent Roux-en-Y gastric bypass and 23% who underwent sleeve gastrectomy remained in remission from type 2 diabetes compared with 2 (5%) in the medical therapy group (thus, Answer C is correct). In the surgical groups, 89% remained off insulin therapy with an average hemoglobin A1c level of 7.0% (53 mmol/mol) compared with 61% of patients in the medical therapy group with an average hemoglobin A1c level of 8.5% (69 mmol/mol).

Educational Objective:

Describe data from randomized controlled trials documenting the remission of diabetes after bariatric surgery.

23.1. A 68-year-old ♂ with osteoarthritis of the knees seeks assistance with weight loss. Height is 178 cm. Weight 143 kg. BMI: 45. He has debilitating joint pain and increasing difficulty with mobility, which he notes is contributing to his weight gain. He wants to pursue knee replacement, but his orthopedic surgeon told him He must lose 20.5 kg. BMI: 39. He also has T2D, stage 3 chronic kidney disease, hypertension, steatotic liver disease, dyslipidemia, and cholelithiasis. His current medications are Metformin, Sitagliptin, Lisinopril, and Atorvastatin. HbA1c: 8.2% (66 mmol/mol). A very low-calorie diet would result in weight loss for this patient, but it may worsen which of the following conditions?

A. Cholelithiasis
B. Dyslipidemia
C. Hypertension
D. Steatotic liver disease
E. Type 2 diabetes

23.2. ANSWER: A) Cholelithiasis

The most effective treatment currently available for weight loss is bariatric surgery. However, aggressive energy restriction with a very low-calorie diet is almost as effective as gastric banding. Very low-calorie diets are restricted to fewer than 800 kcal per day. Very low-calorie diets are high in protein to maximize lean body mass, which may be a problem in this patient with chronic kidney disease. Very low-calorie diets produce, on average, 17% to 18% weight loss over 3 months. However, 25% of patients on such a diet for 2 months develop gallbladder disease, particularly acute cholecystitis due to cholelithiasis (Answer A), frequently requiring surgery (6% of patients on a very low-calorie diet for 2 months require surgery).

The increase in gallbladder disease is thought to be due to decreased gallbladder contractility.

23.2. ANSWER: A) Cholelithiasis: The greater the rate and magnitude of weight loss, the greater the risk of gallbladder disease. This patient already has known gallstones, which would put her at even higher risk for cholecystitis and potentially gallstone pancreatitis. Very low-calorie diets have also been shown to produce dramatic improvements in glucose levels in persons with T2D (thus, Answer E is incorrect). Steatotic liver disease is generally improved with weight loss, particularly with diets lower in fats (thus, Answer D is incorrect), which can also effectively lower triglycerides and improve dyslipidemia (thus, Answer B is incorrect). Hypertension generally improves with weight loss (thus, Answer C is incorrect). Concerns remain about the long-term maintenance of weight loss with this strategy. Long-term weight loss with very low-calorie diets tends to be the same as for low-calorie diets.

Educational Objective:

Counsel patients about the benefits and risks of very low-calorie diets.

24.1. A 59-year-old ♂ has T2D, hypertension, and hyperlipidemia with an LDL 180 mg/dL (4.66 mmol/L). His doctor advised him to start a statin for primary prevention of cardiovascular disease. After starting atorvastatin, 80 mg daily, LDL decreased to 95 mg/dL (2.46 mmol/L). However, he developed pain in his lower extremities, and his creatine kinase level rose to twice the upper normal limit. He stopped the atorvastatin, and the pain resolved. His TSH level is normal.
Which of the following medications should be started now?

A. Evolocumab
B. Ezetimibe
C. Fenofibrate
D. Low-dose rosuvastatin
E. Niacin

24.2. ANSWER: D) Low-dosage rosuvastatin

Myalgias occur in approximately 5% to 10% of patients prescribed statin therapy. This adverse effect is much more prevalent than statin-induced myopathy, which the US FDA defines as a creatine phosphokinase level greater than 10 times the upper normal limit, or rhabdomyolysis, defined as a creatine phosphokinase level greater than 10,000 U/L. Rhabdomyolysis is an emergent condition that warrants the immediate cessation of statin therapy to prevent kidney failure. However, this condition occurs in only 3 per 100,000 person-years Deciding what to do when patients have muscle pain, weakness, or cramps while taking a statin is a difficult clinical problem. Several options are available, and no clear clinical trial data define the best approach. Statins are currently the single best class of medications for cardiovascular disease prevention.

24.3. ANSWER: D) Low-dosage rosuvastatin

As a result, the first goal is to try to keep a patient like this one on the highest tolerated statin dosage. The best first approach is to prescribe a lower dosage of a statin that the patient has not tried before. For the described patient, that would be rosuvastatin (Answer D). Another option is to try alternate-day or weekly statin use. However, no clinical trials show cardiovascular event reduction using this approach. While fenofibrate (Answer C), niacin (Answer E), and ezetimibe (Answer B) can all have favorable effects on serum lipid levels, none has been shown to produce reductions in cardiovascular end points when used as a single agent, so prescribing any one of them would not be the next step until various approaches to prescribing statins have failed.

24.4. ANSWER: D) Low-dosage rosuvastatin

The PCSK9 inhibitors evolocumab (Answer A) and alirocumab are approved by the US FDA for use in patients with clinical atherosclerotic cardiovascular disease and heterozygous familial hyperlipidemia, which this patient does not have. PCSK9 inhibitors have been studied in statin-intolerant patients with LDL-cholesterol levels in this patient's range (GAUSS-1 and GAUSS-2 studies), but statin intolerance alone is not currently an approved indication in the United States in the absence of clinical atherosclerotic cardiovascular disease or familial hyperlipidemia.

Educational Objective:

Recommend options for managing statin-associated muscle pain.

25.1. Current US FDA-approved medications for weight loss include hormone receptor agonists (i.e., liraglutide, semaglutide, and tirzepatide), but many hormones have a role in appetite and weight regulation.

Which of the following hormones would be a good target for a hormone receptor antagonist to stimulate weight loss?

A. Cholecystokinin
B. Ghrelin
C. GLP-1
D. Oxyntomodulin
E. Peptide YY

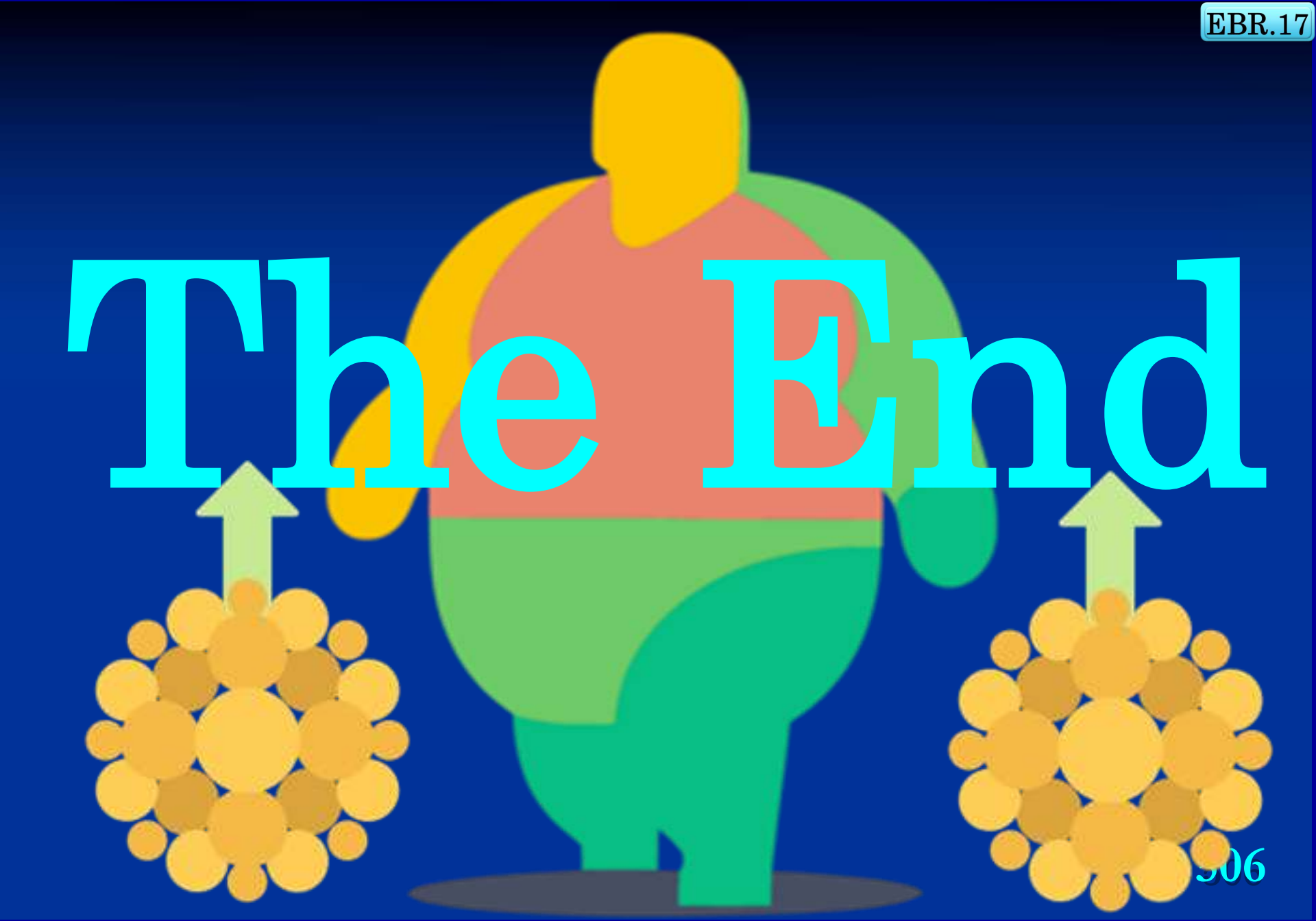
25.2. ANSWER: B) Ghrelin: Many gut hormones act through the circulation and peripheral nervous system (vagal afferents) on the central nervous system pathways, particularly in the hypothalamus and arcuate nucleus, to regulate appetite. Ghrelin (Answer B) is the only hormone listed as an answer choice that stimulates appetite through the NPY-Agouti-related peptide (AgRP) orexigenic neuronal pathways. Ghrelin is secreted by the stomach and rises in the morning after awakening and at regular intervals before each meal, stimulating nutrient intake. Blocking the effects of ghrelin by blocking its receptor should decrease hunger, although such a compound has not been successfully developed to assist with weight loss. All of the hormones listed (GLP-1 [Answer C], cholecystokinin [Answer A], peptide YY [Answer E], and oxyntomodulin [Answer D]) stimulate satiety via anorexigenic signaling through the POMC/CART neuronal pathways.

25.3. ANSWER: B) Ghrelin:

As nutrients pass through the gut, GLP-1 is released from the small intestine, cholecystokinin from the duodenum, and peptide YY from the large intestine. Leptin is secreted by adipose tissue, and circulating levels are directly proportional to adipose tissue mass, signaling adequate fuel stores. Antagonizing the effect of satiety hormones would only serve to make patients hungrier and consume more food.

Educational Objective:

Describe the various hormones affecting appetite regulation and weight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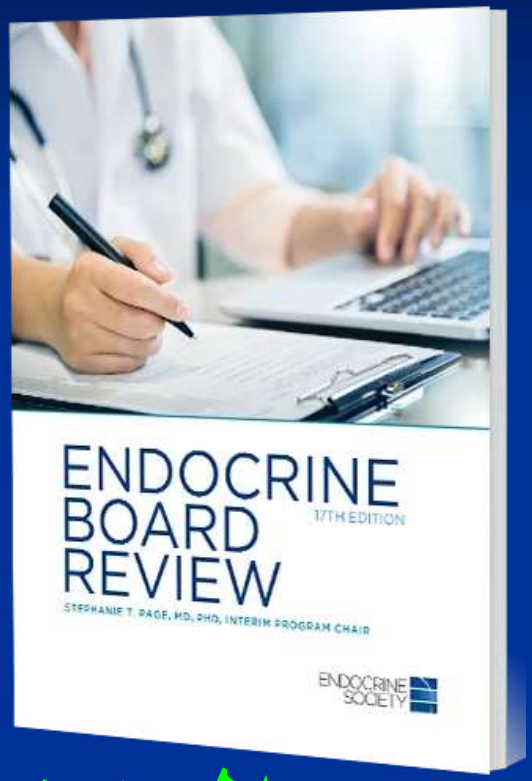
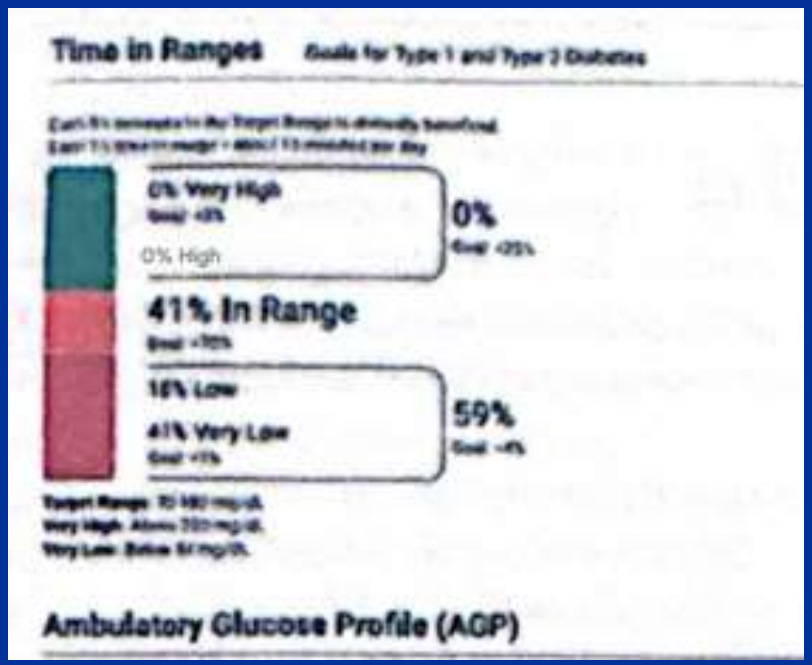
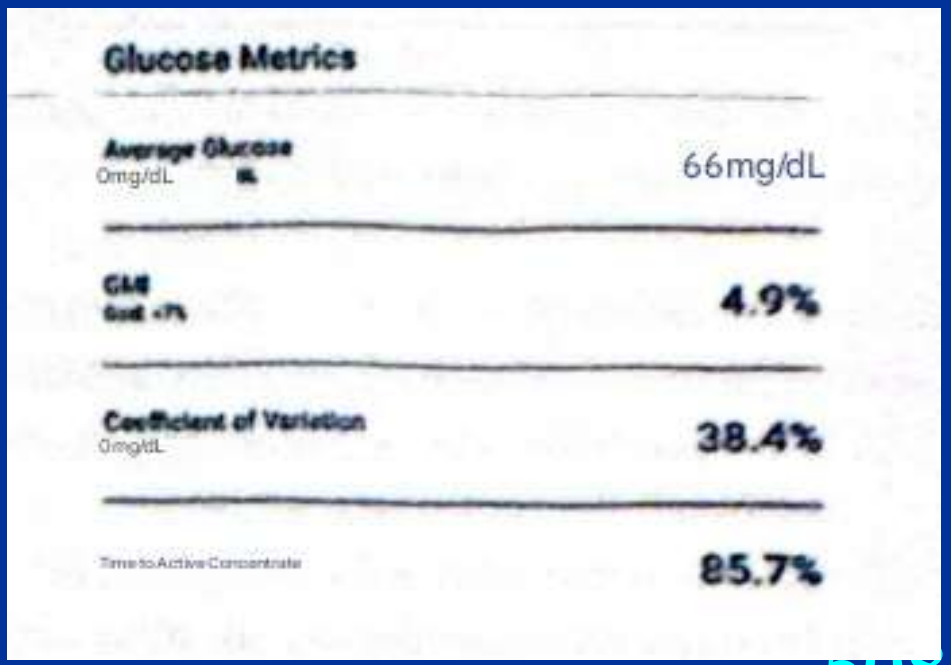


Diabetes 1

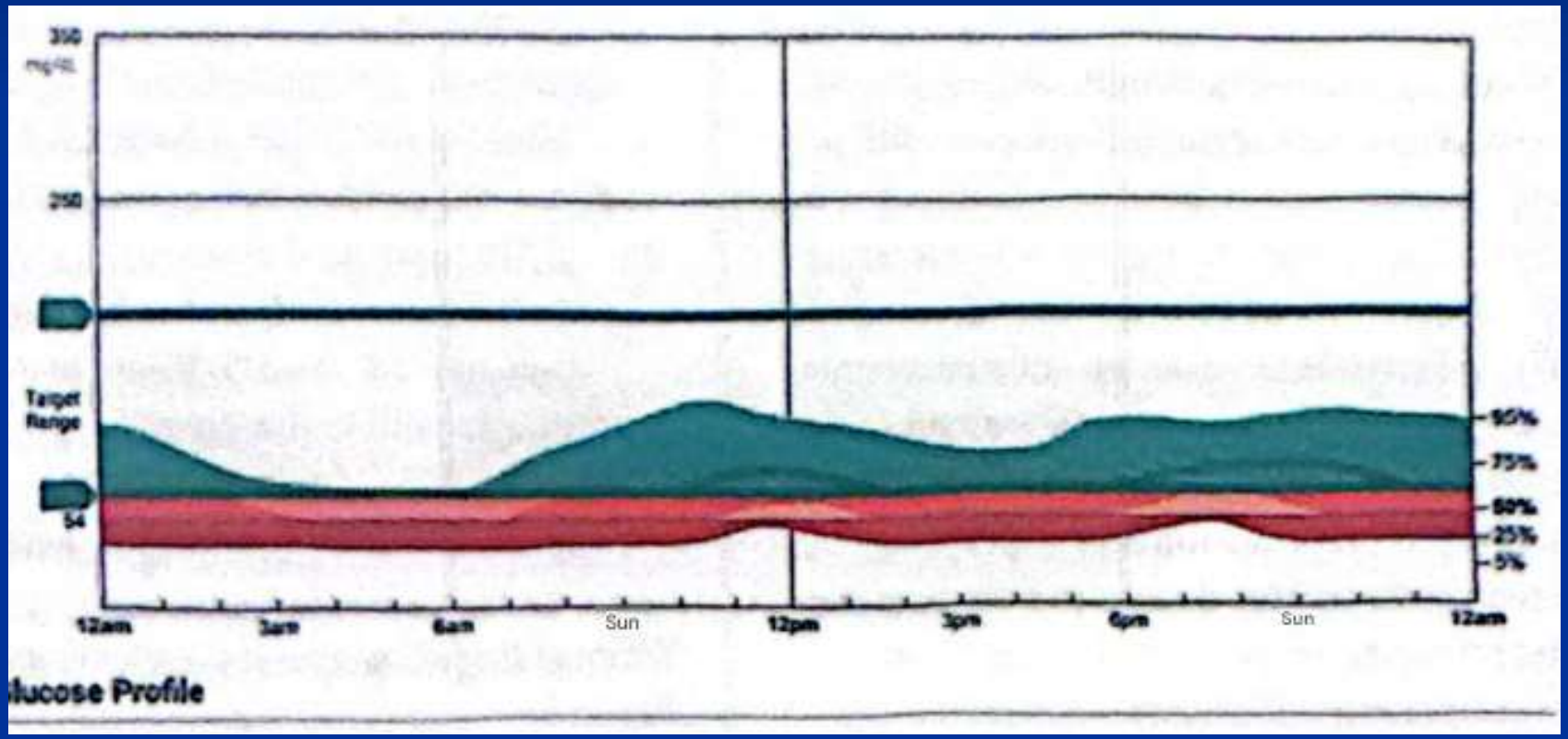
الدكتور محمد الشعباني

1.1. A 27-year-old ♂ is referred for treatment of T1D. He has had diabetes since age 4 and grew up with a single mother who had limited resources. He had suboptimal glycemic control until he reached his mid-20s when he began to focus very intently on his diabetes with a HbA1c level below 6.0% (<42 mmol/mol). He began restricting food and eating a very low-carbohydrate diet

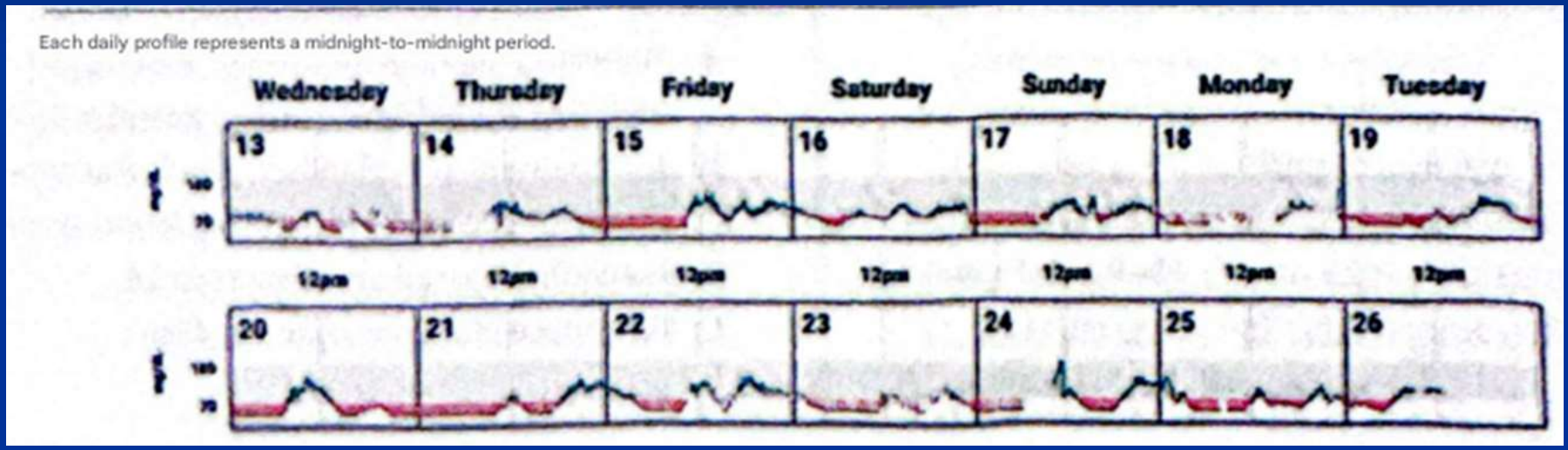




1.2. A 27-year-old ♂ is referred for treatment of T1D.



1.3. A 27-year-old ♂ is referred for treatment of T1D.



1.4. Exam: height: 185 cm. weight: 64 kg. BMI: 18.5. Exam findings are normal. Lab: normal, HbA1c: 4.8% (29 mmol/mol). His current treatment regimen consists of multiple daily insulin injections with insulin degludec, 20 units nightly, and rapid-acting insulin that he doses with a carbohydrate ratio of 1:10 and a correction factor of 1:30. He has not had an episode of level 3 hypoglycemia. He confirms his sensor values with fingerstick glucose measurements. He lives alone and works from home. He says he is much more worried about hyperglycemia than hypoglycemia and does not want to change his insulin doses or his diet. His initial continuous glucose monitor tracing is shown (see image, preceding page). His glucose concentrations have looked essentially the same for the past 12 months. Which is the most likely explanation for this patient's glucose readings?

A. Adrenal insufficiency
B. Eating disorder
C. Excessive exercise
D. Inaccurate sensor readings
E. Insulinoma

1.5. ANSWER: B) Eating disorder

Eating disorders (Answer B) are more common in people with type 1 diabetes than in the general population. They tend to be harder to treat and require a multidisciplinary approach. Often, they lead to hyperglycemia if people underdose insulin for their carbohydrate intake. However, in this case, the patient was both undereating carbohydrates and giving too much insulin.

Individual sensor readings can read falsely low (Answer D), but in this patient's case, many sensors over time yielded the same results. Additionally, he confirmed the continuous glucose monitor results with fingerstick measurements. Aerobic exercise can lower glucose levels, but resistance exercise can raise glucose levels. The constantly low glucose levels seen in this patient would not occur unless someone exercised daily and failed to eat the amount of carbohydrate needed to restore their glucose levels (Answer C).

1.6. ANSWER: B) Eating disorder

Adrenal insufficiency (Answer A) can cause hypoglycemia in people with type 1 diabetes, but it tends to cause episodes of level 3 (severe) hypoglycemia. This patient uses insulin and an extremely low-carbohydrate diet to maintain his glucose levels in a range where he does not have disabling episodes of hypoglycemia. He has no physical or metabolic findings of adrenal insufficiency—no weight loss, hyperpigmentation, or abnormal laboratory values. Symptomatic insulinoma (Answer E) would be extremely rare in someone with type 1 diabetes. His type 1 diabetes autoimmune response would likely destroy any insulin-producing cells. Additionally, he would likely have episodes of symptomatic hypoglycemia if he had an insulinoma

Educational Objective:

Explain the role of psychosocial factors in the etiology of hypoglycemia and their interaction with disordered eating patterns.

2.1. A 20-year-old college ♀ had islet-cell antibodies assessed because her younger sister recently developed T1D. The patient's glutamic acid decarboxylase antibody measurement is 33 units/mL (normal <5 units/mL). ZnT8 antibodies, insulin autoantibodies, and IA2 antibodies are undetectable. Results of a 75-g oral glucose tolerance test:
Fasting plasma glucose = 96 mg/dL (SI: 5.3 mmol/L)
1-hour = 183 mg/dL (SI: 10.2 mmol/L)
2-hour = 134 mg/dL (SI: 7.4 mmol/L)
Based on the American Diabetes Association criteria, which of the following best classifies her current glycemic condition?

A. Impaired glucose tolerance
B. Normoglycemia
C. Type 1 diabetes, stage 1
D. Type 1 diabetes, stage 2
E. Type 1 diabetes, stage 3

2.2. ANSWER: B) Normoglycemia According to the American Diabetes Association

Association Standards of Care in Type 1 Diabetes, Stage 1 requires the presence of 2 or more autoantibodies and normal glycemia. Stage 2 requires 2 or more autoantibodies plus dysglycemia (prediabetes). Stage 3 is defined by glucose levels consistent with a diabetes diagnosis (see table, following pages). This patient has 1 positive autoantibody and normal glucose tolerance as Determined by oral glucose tolerance testing using a fasting and a 2-hour value. He has normoglycemia (Answer B). The patient's values do not fit the criteria for a diagnosis of any stage of T1D (Answers C, D, and E). Her laboratory values do not meet glycemic criteria for prediabetes (either impaired glucose tolerance [Answer A] or impaired fasting glucose).

Educational Objective:

Differentiate among the stages of type 1 diabetes.

Table 2.2—Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

Table 2.4—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG, normal A1C	• Islet autoantibodies (usually multiple) • Dysglycemia: ○ IFG: FPG 100–125 mg/dL (5.6–6.9 mmol/L) or ○ IGT: 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) or ○ A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

Adapted from Skyler et al. (35). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (82). Dysglycemia can be defined by one or more criteria as outlined in the table.

3.1. A 24-year-old ♀ has an identical twin who developed T1D approximately 1 year ago. The patient had laboratory testing done to evaluate whether she is developing T1D and if she is eligible for teplizumab therapy. She has 2 positive islet-cell antibodies, a HbA1c 6.1% (43 mmol/mol), and a fasting plasma glucose value of 116 mg/dL (6.4 mmol/L).

Which of the following is the best recommendation now?

A. Measure fasting glucose and C-peptide to assess residual A-cell function
B. Perform oral glucose tolerance testing
C. Repeat hemoglobin A measurement
D. Repeat laboratory tests within the next 6 weeks to verify their accuracy.
E. Start teplizumab treatment without further testing.

3.2. ANSWER: E) Start teplizumab treatment without further testing

Teplizumab therapy (Answer E) is approved for the treatment of stage 2 type 1 diabetes. Teplizumab is an option if a patient has laboratory values that diagnose stage 2 type 1 diabetes, as is the case in this vignette. To definitively answer the question as to whether this patient has stage 3 type 1 diabetes, oral glucose tolerance testing (Answer B) would need to be done, but this is not necessary to start teplizumab outside of a clinical trial.

A repeat HbA1c measurement now (Answer C) is not needed, and repeating laboratory tests in 6 weeks and holding off on treatment (Answer D) is not necessary. Treatment should begin as soon as possible.

C-peptide levels (Answer A) are not part of the criteria for determining whether a person has prediabetes or diabetes.

Educational Objective:

Use criteria to determine whether initiation of teplizumab therapy is appropriate.

4.1. A 26-year-old ♂ with HIV is about to start antiretroviral therapy. He has no history of prediabetes or diabetes.
Which of the following is the recommended approach to screen for the development of abnormal glucose tolerance in this patient?

Answer	Before starting antiretroviral therapy	Follow up screening
A	Measure fasting glucose and HbA1c	Measure fasting glucose and HbA1c
B	Measure fasting glucose	Measure fasting glucose annually
C	Measure fasting glucose	Measure fasting glucose 3-6 months after starting/switching antiretroviral therapy and annually thereafter
D	Perform 75 g oral glucose tolerance test	Measure fasting glucose 3-6 months after starting/switching antiretroviral therapy

4.2. ANSWER: C) Measure fasting glucose

before starting antiretroviral therapy, 3-6 months after starting/switching antiretroviral therapy, and annually thereafter. Patients with HIV are at higher risk for developing prediabetes and diabetes. Some antiretroviral therapies can increase this risk. New-onset diabetes occurs in more than 5% of patients infected with HIV who are taking protease inhibitors, and more than 15% develop prediabetes. Therefore, screening programs for prediabetes and diabetes should be implemented. Because hemoglobin A1c measurement may underestimate glycemia levels in people with HIV, fasting plasma Glucose measurement is preferred for diagnosing prediabetes and diabetes in these individuals.

Answers A, B, and D do not describe the currently recommended testing protocol.

Educational Objective

Screen for prediabetes and diabetes in individuals with HIV who are on antiretroviral regimens.

5.1. A ♀ with prediabetes wants to start metformin to prevent progression to T2D (off-label but suggested by the American Diabetes Association).
Based on data from the Diabetes Prevention Program, which of the following characteristics is most likely to predict response to the addition of Metformin?

A. Age >59 years
B. BMI >30 kg/m^2
C. Fasting plasma glucose of 100-110 mg/dL (5.6–6.1 mmol/L)
D. History of gestational diabetes
E. Positive family history for T2D

5.2. ANSWER: D) History of gestational diabetes

Metformin is not FDA-approved to treat prediabetes, but it is commonly used as suggested by the American Diabetes Association in individuals at the highest risk for developing diabetes. This recommendation comes from the Diabetes Prevention Program, where metformin was compared with intensive lifestyle intervention versus placebo. The study lasted for about 3 years. Participants have now been followed for at least 15 years in the Diabetes Prevention Program Outcomes Study (DPPOS). In the DPP, lifestyle change reduced the rates of developing diabetes by 58% compared with rates in the placebo arm. In people who took metformin, the risk of developing type 2 diabetes was reduced by 31%. Metformin was most effective in women with a history of gestational diabetes (Answer D), people between the ages of 25 and 44 years (therefore, Answer A is incorrect), and those with a BMI greater than 35 kg/m^2 (therefore, Answer B is incorrect). Older individuals responded less favorably to metformin than younger individuals. People with a higher fasting glucose level (>110 mg/dL (>6.1 mmol/L)) responded better to metformin than those with a lower fasting glucose level (therefore, Answer C is incorrect). A positive family history of type 2 diabetes did not portend a response to metformin (therefore, Answer E is incorrect).

Educational Objective:

Identify appropriate candidates for the use of metformin in diabetes prevention.

6.1. In an asymptomatic person with T1D, on no medication other than insulin and with no additional medical problems, which of the following should be measured annually?

A. Celiac antibodies
B. TPO antibodies
C. TSH
D. Vitamin B12

6.2. ANSWER: C) TSH

Although individuals with type 1 diabetes are at increased risk for other types of autoimmunity, current recommendations do not call for testing additional autoantibodies (Answers A and B) (except at baseline) unless they are symptomatic. However, TSH (Answer C) should be measured annually to assess basic thyroid function.

Assessing for vitamin B1 deficiency (Answer D) would not apply to someone with type 1 diabetes unless they had celiac disease or were on metformin, neither of which applies to this patient.

Educational Objective:

Describe annual laboratory screening guidelines in people with type 1 diabetes.

7.1. A 68-year-old ♂ with T2D is planning a 24-hour fast for religious reasons. He is allowed to drink water during his fast but may not consume food. His eGFR is 62 mL/min per 1.73 m^2. He takes Semaglutide; insulin Glargine, 20 U at bedtime; an angiotensin II receptor blocker; a calcium channel blocker; a diuretic; and a Statin. HbA1c 7.1% (54 mmol/mol), and he intermittently wears a continuous glucose monitor. He has fasted in the past, but that was before he was on insulin.

In addition to wearing his continuous glucose monitor, which of the following is the best recommendation?

A. Hold all medications the morning of the fast
B. Hold his SGLT-2 inhibitor the morning of the fast
C. Not fast due to medical reasons
D. Reduce his insulin dose the night before the fast

7.2. ANSWER: D) Reduce his insulin dose the night before the fast

When a person with diabetes prepares for fasting, the most important factor to consider is whether they are taking medication(s) that can cause hypoglycemia. If they are, that medication must be stopped or the dosage reduced. Additionally,

Education should be provided regarding how to prevent/treat hypoglycemia should it occur. Of the medications he is taking, insulin is the one that can cause hypoglycemia. Reducing the dose the night before fasting (Answer D) would help him avoid hypoglycemia the next day. His daytime glucose levels are likely mostly in the target range based on his hemoglobin A1c value. The degree of dose reduction is largely based on the patient's clinical sense. For some, a 100% reduction is reasonable; for others, a 60% to 80% reduction is adequate.

7.3. ANSWER: D) Reduce his insulin dose the night before the fast

Stopping all medications the morning of the fast (Answer A) is generally not necessary if the medications do not cause hypoglycemia. If a person is doing well on SGLT-2 inhibitor therapy, there is no medical reason to stop it when fasting (Answer B), unless the patient is unable to drink fluids. Diabetic ketoacidosis is rare in people with type 2 diabetes, and it has not been shown to occur in people on SGLT-2 inhibitor therapy during religious fasting

When fasting is for religious reasons, it is often very important for the individual to be able to participate in this practice. Therefore, attempts should be made to safely accommodate it (thus, Answer C is incorrect). However, if fasting is not possible, many religions offer medical exemptions for those who cannot tolerate it.

Educational Objective:

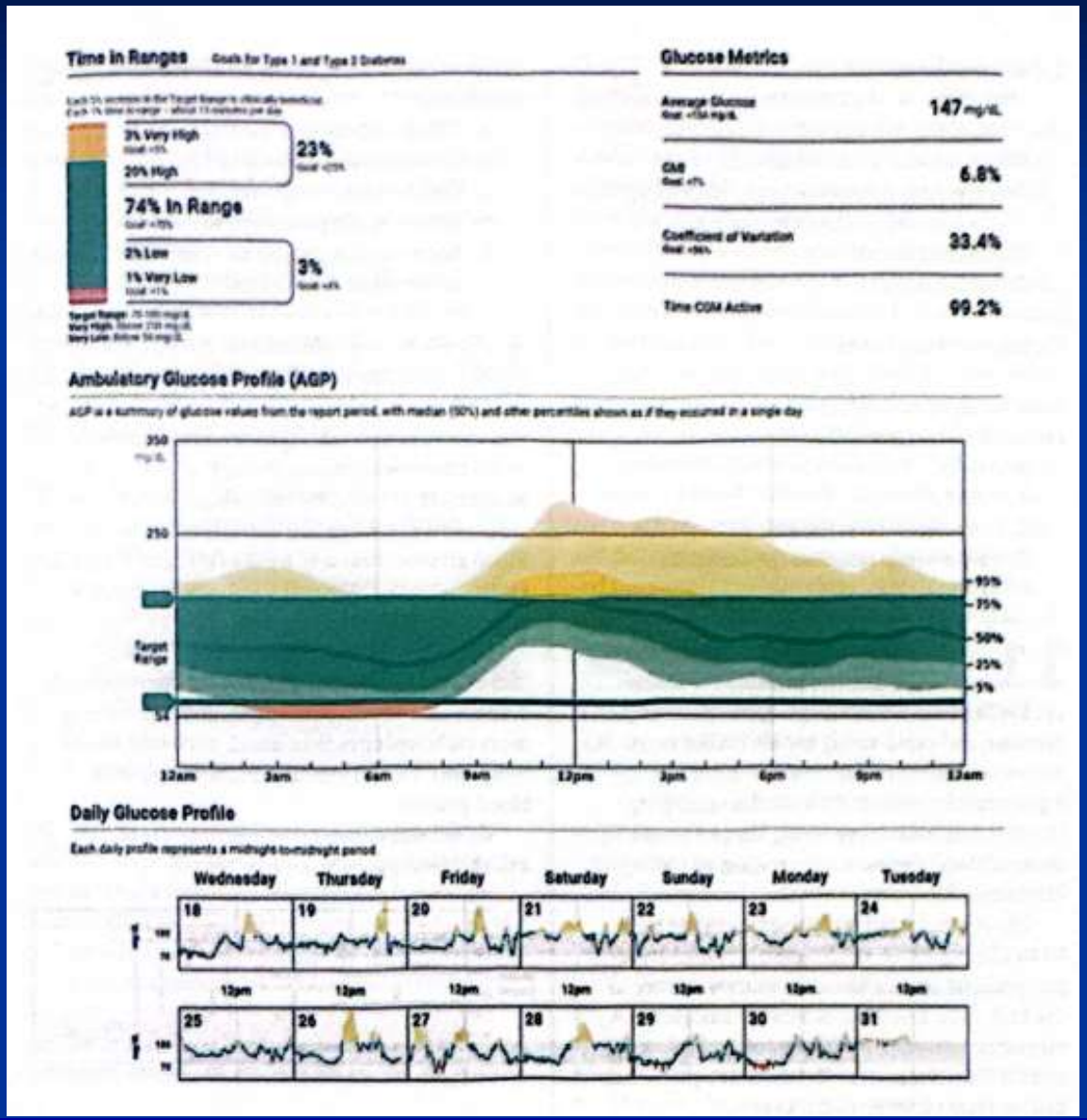
Adjust diabetes medications before religious fasting.

8.1. A 33-year-old woman with T1D wants to try automated insulin delivery therapy. She is currently on a multiple-daily insulin injection regimen plus continuous glucose monitoring. HbA1c: 6.8-7.2% (51-55 mmol/mol) with a time-in-range of 72%. Ambulatory glucose profile is shown (see image, following page). She is considering pregnancy within the next 6 months.

When discussing the features of automated insulin delivery systems with this patient, which of the following is most accurate?

A. Administration of premeal bolus doses is not needed with most automated insulin delivery systems.
B. Automated insulin delivery systems are approved for use in pregnancy.
C. Episodes of severe (level 3) hypoglycemia are eliminated by automated insulin delivery.
D. The most predictable outcome would be an improvement of her overnight glucose levels

8.2. A 33-year-old woman with T1D



8.3. ANSWER: D) The most predictable: outcome would be improvement of her overnight glucose levels. In every study assessing the benefits of automated insulin delivery systems of any type, the greatest benefit from the automation is seen overnight (Answer D), when the person with diabetes is not eating. It is during this time when the time-in-range is the highest, partly due to the lack of variability seen when a person is not consuming calories. Other features, such as the type and extent of autocorrect bolus doses and target ranges, differ among systems. Currently, most available automated insulin delivery systems require premeal bolus doses for optimal performance (thus, Answer A is incorrect). Episodes of level 1, 2, and 3 hypoglycemia can still occur while on single-hormone automated insulin delivery systems (thus, Answer C is incorrect).

Target settings for pregnancy are not available in most automated insulin delivery systems and therefore they are not approved for use in pregnancy (thus, Answer B is incorrect). To reach pregnancy targets, people with type 1 diabetes may need to exit automode and use manual mode for tighter target goals.

Educational Objective:

Counsel patients with type 1 diabetes on the most likely benefits from using automated insulin delivery systems.

9.1. A 62-year-old ♂ with a history of T2D since age 41 asks for advice about the type of eye exam he should have. He has had no diabetic retinopathy observed on yearly dilated retinal examinations. His last retinal exam was 1 year ago, and he would prefer not to have his eyes dilated frequently since it causes significant discomfort. He has no other ophthalmologic issues. HbA1c: 6.4% (46 mmol/mol) in recent years while on Semaglutide, an SGLT-2 inhibitor, and Metformin. Which is the best recommendation regarding eye exam for this patient?

A. Dilated eye exam annually by an ophthalmologist because of Semaglutide use
B. Dilated eye exam annually by an optometrist
C. No further screening for diabetic retinopathy since he has had diabetes for > 20 years
D. Retinal photography annually with remote reading or FDA-approved artificial intelligence technology

9.2. ANSWER: D) Retinal photography 9 years annually with remote reading or FDA-approved artificial intelligence technology: Technology has advanced enough that in certain settings, retinal photography (Answer D) can be used in place of a dilated eye exam. Several artificial intelligence platforms have been approved by the FDA for diabetic retinopathy screening and examination. Therefore, this patient could find a center where such technology is available. The longer the duration of diabetes, the greater the risk for retinopathy. Although tight glucose control reduces the risk considerably, this patient still requires screening (thus, Answer C is incorrect). With no history of retinopathy and a stable hemoglobin A level below 7.0% (<53 mmol/mol), this patient does not need to have an annual dilated eye exam (Answers A and B) to assess for diabetic retinopathy. Semaglutide has not been shown to cause retinopathy, particularly not in people without preexisting retinopathy. In one clinical trial, an increased rate of treatment-requiring retinopathy was observed with semaglutide, seemingly because hemoglobin A levels were lowered too rapidly in people with preexisting retinopathy.

Educational Objective:

Recommend retinopathy screening in an individual with well-controlled diabetes and no preexisting retinopathy

10.1. An 18-year-old ♀ seeks advice for erratic blood glucose values. T1D was diagnosed two years ago, and a regimen of basal and mealtime insulins was initiated. Her glycemic control has always been adequate, with hemoglobin A values around 7.0% (53 mmol/mol). However, a few weeks ago, she started noticing unpredictable blood glucose values with recurrent hypoglycemic episodes (blood glucose, 45-60 mg/dL [2.5-3.3 mmol/L]). These episodes have occurred mainly after meals and have been accompanied by symptoms. Despite eating more snacks to prevent hypoglycemia, she has lost 1.8 kg in the past two weeks. She has no gastrointestinal concerns or dizziness. Her menses are regular. Medications: insulin glargine and lispro. Exam: BP: 110/70. BMI: 22. Exam: findings are unremarkable Lab: HbA1c: 6.7% (4.0%-5.6%) (50 mmol/mol). TSH 1.1 mIU/L (0.5-5). Serum cortisol (random) 11 µg/dL (5-25 µg/dL) (303.5 nmol/L [137.9-689.7 nmol/L]). Electrolytes, normal. Cr: normal. Further workup is done.
An elevation of which would most likely explain her hypoglycemia?

A. ACTH
B. FT4
C. Glutamic acid decarboxylase 65 antibodies
D. Tissue transglutaminase IgA antibodies
E. 21-Hydroxylase antibodies

10.2. ANSWER: D) Tissue transglutaminase IgA antibodies

About 5% of persons with T1D develop celiac disease. Only a minority of children and adolescents with type 1 diabetes and celiac disease present with gastrointestinal symptoms. More common initial findings include unpredictable blood glucose measurements and recurrent episodes of hypoglycemia due to erratic intestinal absorption of nutrients. Thus, elevated tissue transglutaminase IgA antibodies (Answer D) would most likely explain her hypoglycemia. < 1% of children with T1D have autoimmune adrenalitis (Addison's disease) (Answer A). In one report, about 2% of children with type 1 diabetes had circulating antibodies to steroid 21-hydroxylase (Answer E). Although less common than celiac disease, this condition is associated with decreased insulin requirement and increased frequency of hypoglycemia, hyperpigmentation, hypotension, hyponatremia, and hyperkalemia (none of which is present in this patient).

10.3. ANSWER: D) Tissue transglutaminase IgA antibodies

Hyperthyroidism (Answer B) is rare in patients with type 1 diabetes (1%–2%) and can lead to higher blood glucose values due to insulin resistance, not hypoglycemia. In addition, except for weight loss, this patient has no symptoms or physical findings to suggest Graves' disease

Antibodies to glutamic acid decarboxylase (a 65-kJ protein) (Answer C) are found in about 70% of patients with type 1 diabetes at the time of diagnosis. They could very well be high in this patient, but this would not explain her hypoglycemia.

Educational Objective:

Identify hypoglycemia resulting from celiac disease in type 1 diabetes and describe its presentation.

11.1. A 26-year-old man with a 6-year history of T1D presents for follow-up. He has been on insulin glargine, 20 U at bedtime, and rapid-acting insulin before meals. His insulin-to-carbohydrate ratio is 1 unit for every 8 g of carbohydrate, and his insulin sensitivity factor is 1 unit for every 30 mg/dL (1.7 mmol/L) above a blood glucose concentration of 100 mg/dL (5.6 mmol/L). Fasting blood glucose values range from 80-130 mg/dL (4.4–7.2 mmol/L). 2-hour postprandial blood glucose measurements are in the high 100s, low 200s. A recent HbA1c: 7.6% (60 mmol/mol), down from 8.4% (68 mmol/mol) 4 months ago. He has had no recent hypoglycemic events. His main concern is a 4.5-kg weight gain that has occurred with improved glycemic control over the past year. He prefers not to switch to an insulin pump or to use a continuous glucose sensor. He does not want to increase his insulin requirements at meals because of fear of additional weight gain.

Pramlintide is recommended before meals; it is the only non-insulin glycemic therapy that is FDA-approved for use in T1D.

Which of the following should be advised upon starting pramlintide?

A. Change carbohydrate ratio to 1:16
B. Change sensitivity factor to 1:60
C. Continue the same insulin regimen
D. Reduce insulin glargine to 10 units
E. Reduce insulin glargine to 10 units and change carbohydrate ratio to 1:16

11.2. ANSWER: A) Change carbohydrate ratio to 1:16

When initiating pramlintide, the current mealtime
The insulin dose should be reduced by 50% to avoid hypoglycemia. Pramlintide is a synthetic analogue of human amylin cosecreted with insulin by pancreatic cells. Pramlintide reduces postprandial glucose increases via the following mechanisms: (1) prolongation of gastric emptying time, (2) reduction of postprandial glucagon secretion, and (3) reduction of caloric intake through centrally mediated appetite suppression. The main adverse effect is nausea (28%–48%), which can be alleviated by slow titration of the drug. This patient's carbohydrate intake will likely be reduced when pramlintide is started, and in anticipation of this, increasing their carbohydrate ratio (Answer A) will help prevent hypoglycemic episodes. Basal insulin and sensitivity factors should not be changed (therefore, Answers B, D, and E are incorrect).

Educational Objective:

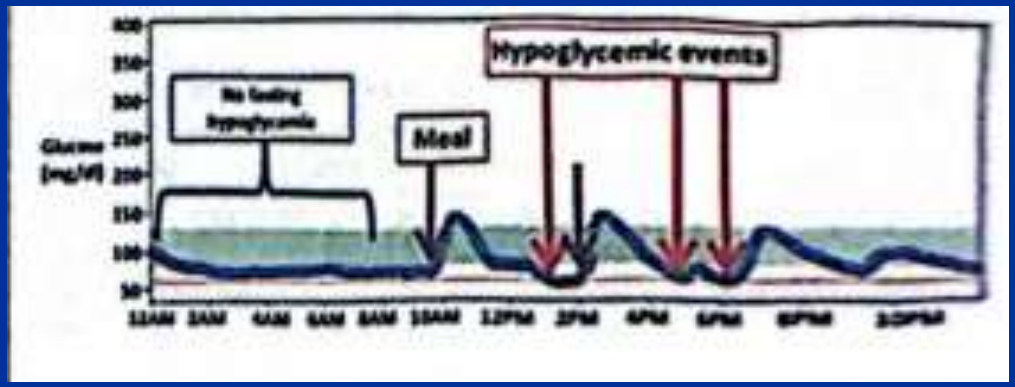
Correctly prescribe pramlintide and reduce the mealtime insulin dose upon initiation

12.1. A 63-year-old ♂ with T2D had Roux-en-Y gastric bypass 18 months ago. After gastric bypass, he lost 23 kg and was able to stop insulin therapy. He is currently on no antihyperglycemic therapy. He has been admitted to the hospital following a seizure. His wife called 911 when she found him confused. Blood glucose measured by the emergency medical technicians was 23 mg/dL (1.3 mmol/L), and he responded to treatment with D50. For about two months, he has been feeling groggy and not thinking clearly for approximately two hours after meals, particularly after consuming more carbohydrates than usual. Juice relieves the symptoms. He infrequently checks his fingerstick blood glucose.

Continuous glucose monitoring is initiated, and the results are shown (see image):

In conjunction with a controlled portion, low-glycemic index carbohydrate diet (<30 g/meal, 15 g per snack), which addition to his diabetes medication regimen should be considered as a next step for hypoglycemia management?

A. Acarbose
B. Diazoxide
C. Liraglutide
D. Metformin
E. Octreotide



12.2. ANSWER: A) Acarbose: Late postbariatric hypoglycemia occurs most commonly in patients who have undergone Roux-en-Y gastric bypass. Spikes in glucose due to rapid gastric emptying, vigorous insulin secretion, reduced insulin clearance and insulin-independent glucose uptake, and high levels of GLP-1 all contribute to the phenomenon of late postbariatric hypoglycemia. If medical nutrition therapy with a low-glycemic index meal plan does not enable control of the hypoglycemia, other medications can be added to the regimen. α-Glucosidase inhibitors (Answer A) slow postprandial glucose absorption and reduce postmeal blood glucose spikes and insulin secretion. Slow introduction and escalation in dosage can help avoid the adverse effects of gastrointestinal discomfort. Octreotide (Answer E), which reduces incretin and insulin secretion, can also be administered; however, its use may be limited by high cost and adverse effects, including diarrhea, steatorrhea, and acute hypoglycemia, most likely due to inhibition of insulin secretion. Diazoxide (Answer B) reduces insulin secretion, so it may also be used, but it can lead to fluid retention and headaches. Reports on the efficacy of GLP-1 receptor agonists (Answer C) in this setting have been variable. Finally, metformin (Answer D) absorption and bioavailability seem to be higher after gastric bypass, and this may have implications for dosing and toxicity risk.

Note: Continuous glucose monitoring image reprinted from Patti ME. Hypoglycemia after bariatric surgery. Meet the Professor Endocrine Case Management. Presented at ENDO in Chicago, Illinois. March 2018.

Educational Objective

Explain the rationale and strategies for management of late postbariatric hypoglycemia.

13.1. 13. A 35-year-old man has a 15-year history of T1D complicated by nonproliferative diabetic retinopathy. He is concerned about kidney complications of diabetes. HbA1c: 7.8% (62 mmol/mol) on insulin glargine and mealtime rapid-acting insulin. Two separate measurements of his urine alb/Cr ratio are 20 and 12 mg/g Cr. eGFR 82 mL/min/1.73 m^2 (> 60).

Exam: BP: 128/72. BMI: 24.

Which is the most effective approach to reduce future risk of clinically significant diabetic nephropathy in this patient?

A. Advise a reduction in his dietary protein intake to <0.5 g/kg/day
B. Lower his BP: to <120/70 mm Hg
C. Lower his HbA1c <7.0% (<53 mmol/mol)
D. Start losartan
E. Start ramipril

13.2. ANSWER: C) Lower his hemoglobin A to <7.0% (<53 mmol/mol)

Glycemic control has clearly been shown to decrease the risk of onset or progression of diabetic nephropathy in patients with type 1 diabetes. Thus, lowering his hemoglobin A_1 to less than 7.0% (<53 mmol/mol) (Answer C) is correct.

In patients with diabetes complicated by either albuminuria or hypertension, the use of either an ACE inhibitor or an angiotensin-receptor blocker as first-line therapy is recommended (in nonpregnant patients). Because this patient has neither albuminuria nor hypertension, there are no data to support the use of an ACE inhibitor (Answer E) or an angiotensin-receptor blocker (Answer D).

Blood pressure control (<140/90 mmHg), glycemic control, and limiting protein intake to 0.8 g/kg per day (the recommended daily allowance) may be recommended. However, there is no additional benefit to lowering his blood pressure to less than 120/70 mmHg (Answer B). Reducing this patient's protein intake to less than 0.5 g/kg per day (Answer A) is not recommended because it would not alter glycemic measures, cardiovascular risk measures, or the course of glomerular filtration rate decline.

Educational Objective:

Recommend interventions to decrease the risk of future diabetic nephropathy in a normoalbuminuric, normotensive patient with type 1 diabetes.

14.1. A 68-year-old man with longstanding type 2 diabetes and peripheral neuropathy presents for a follow-up visit. He has had a right plantar ulcer in the past. HbA1c: 7.6% (60 mmol/mol) on oral antidiabetic agents.

Exam: he has absent sensation to a 10-g monofilament, absent ankle reflexes, callus formation on the plantar aspect of the second and third metatarsal heads, and absent pedal pulses.

Which is the strongest predictor of the development of future foot ulcers in this patient?

A. Abnormal monofilament testing
B. Absent ankle reflexes
C. Absent pedal pulses
D. Callus formation
E. History of previous ulceration

14.2. ANSWER: E) History of previous ulceration

The lifetime risk of developing a foot ulcer in persons with diabetes is about 25%. Multiple factors are associated with an increased risk of ulceration, including previous ulceration or amputation, the presence of peripheral neuropathy with loss of protective sensation, foot deformity, and suboptimally controlled diabetes. The strongest predictive factor is a history of previous ulceration (Answer E), with an odds ratio of 56.8 and up to a 10-fold increased risk for amputation. Other factors are absent ankle reflexes (Answer B) associated with neuropathy (odds ratio, 6.48).

Abnormal response to monofilament testing (Answer A) (odds ratio, 18.42), and male gender (odds ratio, 2.15).

Peripheral vascular disease (Answer C)

is an important prognostic factor for delayed wound healing and amputations but not a strong independent predictor of foot ulceration.

Callus formation (Answer D) does not predispose to foot ulcers.

Educational Objective:

Identify predictors of increased risk of foot ulcers.

15.1. A 34-year-old ♂ with T1D is in the clinic waiting room when the receptionist notes that he seems confused when his name is called, speaks with slurred words, and is unable to follow commands. He is found to have a fingerstick blood glucose value of 39 mg/dL (2.2 mmol/L). After recovery with oral glucose, he reports that despite careful monitoring, including the use of his real-time continuous glucose monitor, he has been losing his ability to sense low blood glucose levels and has had five or six episodes of hypoglycemia with blood glucose values between 40 and 50 mg/dL (2.2–2.8 mmol/L). During one of these episodes, a coworker had to call the paramedics for treatment. HbA1c: 5.9% (41 mmol/mol), and his treatment regimen consists of multiple daily insulin injections and daily exercise in the evening. He lives alone and has worked hard to achieve a HbA1c < 6% (<42 mmol/mol) out of fear of developing diabetes-related complications. Which is the most important immediate next step in this patient's care?

A. Begin using an automated insulin delivery system for insulin administration
B. Instruct him to always carry a glucagon emergency kit
C. Recommend attending a diabetes education class focused on hypoglycemia avoidance
D. Suggest he stop exercising
E. Temporarily relax his tight glucose targets

15.2. ANSWER: E) Temporarily relax his tight glucose targets

Up to 30% of patients with type 1 or longstanding type 2 diabetes have impaired or absent. Hypoglycemia awareness. As plasma glucose levels fall, compromised physiologic counterregulatory defenses include failure of an increase in glucagon secretion and attenuated epinephrine secretion. This, together with the inability to reduce circulating insulin levels, results in the clinical syndrome of Defective counterregulation, which markedly increases the risk of recurrent severe hypoglycemia. Hypoglycemia-attenuating defense against subsequent hypoglycemia is a concept referred to as hypoglycemia-associated autonomic failure (HAAF). The mainstay therapy for HAAF is the scrupulous avoidance of hypoglycemia. Patients with hypoglycemia unawareness and/or severe hypoglycemia and tight control should be advised to relax their glucose targets for a period to allow awareness to potentially return with adrenergic symptoms (Answer E).

15.3. ANSWER: E) Temporarily relax his tight glucose targets

A glucagon emergency kit (Answer B) should be available, but it would not help if he were alone. Additionally, it should only be used as a last resort and would not address the hypoglycemia unawareness

Although a hybrid closed-loop system (Answer A) may help reduce hypoglycemia, it would not address the underlying cause of hypoglycemia unawareness or guarantee its avoidance. There would also be a delay in initiating pump therapy and a learning curve regarding its use. Finally, hybrid closed-loop therapy has not been shown to reduce the number of episodes of severe hypoglycemia, although it can help reduce overt hypoglycemia in certain populations.

While a number of educational programs focusing on hypoglycemia detection and avoidance (Answer C) (Dose Adjustment for Normal Eating [DAFNE], Blood Glucose Awareness Training [BGAT

15.4. ANSWER: E) Temporarily relax his tight glucose targets

Hypoglycemia Awareness and Avoidance [HAAT]) have demonstrated effectiveness in reducing the occurrence of hypoglycemia, such an education program is not the most immediate fix for the patient, but it would be an important part of their subsequent follow-up. Additionally, most programs are not available as stand-alone options in the United States. Lastly, although exercise in people with type 1 diabetes can cause hypoglycemia, the timing and type of exercise influence its effect. Therefore, discussing how to exercise without causing hypoglycemia is important and can generally be accomplished without stopping exercise completely (Answer D).

Educational Objective:

Recommend management of severe hypoglycemia and hypoglycemia unawareness in type 1 diabetes.

16.1. He has had 16 suboptimally controlled T2D for 21 years. She was recently found to have decreased visual acuity ascribed to diffuse proliferative diabetic retinopathy and ischemia on retinal exam. She has housing and food insecurity and is only intermittently able to work. She frequently misses her clinic appointments.
Which treatments should she undergo given her current situation?

A. Focal laser photocoagulation
B. Panretinal laser photocoagulation
C. Ranibizumab injections
D. Vitrectomy

16.2. ANSWER: B) Panretinal laser photocoagulation: Diabetic retinopathy, one of the most common microvascular complications in both T1D and T2D, is classified as non-proliferative when it consists of retinal microhemorrhages and hard exudates, the latter representing lipid deposition. With progressive ischemia, more ominous signs occur, such as ischemic infarcts (cotton wool spots) and neovascularization. In the setting of neovascularization, classified as proliferative retinopathy, panretinal laser photocoagulation (Answer B) has been demonstrated to protect against vision loss Although antivascular endothelial growth factor (anti-VEGF) therapies have largely taken the place of panretinal laser photocoagulation, a prerequisite is the need for consistent, frequent follow-up. Focal laser photocoagulation (Answer A) is typically used for isolated areas of neovascularization. Anti-VEGF drugs, such as ranibizumab (Answer C), are commonly used to treat diabetic retinopathy, but they require consistent follow-up to be effective. Vitrectomy (Answer D) is performed in patients with severe vision loss from severe proliferative diabetic retinopathy after vitreous hemorrhage and severe fibrous changes have developed. It is not a first-line therapy.

Educational Objective:

Recommend appropriate management of diabetic retinopathy based on the patient's clinical characteristics and social determinants of health.

17.1. A 64-year-old ♀ with an 18-year history of suboptimally controlled T2D presents to the emergency department with a 1-week history of left-sided flank pain. She has no fever, chills, dysuria, nausea, postprandial pain, or change in bowel habits. Her medical history is notable for retinopathy requiring laser photocoagulation and distal somatosensory neuropathy. She has had two toe amputations, coronary artery bypass surgery, and right femoral popliteal bypass surgery. Exam: she is afebrile. The left flank and left upper quadrant are exquisitely tender to superficial palpation. Muscle strength is normal in the legs, and sensation is reduced below the knees and absent in the feet. There is no rash. Lab: Fecal occult blood screening, negative. Urinalysis, 2+ protein and 3-5 RBC/high-power field. WBC: 7200/µL (4500-11,000). with normal differential. Chemistry panel, normal. Liver function tests, normal. Amylase and lipase, normal. Abdominal CT is negative for urinary or biliary calcification, and there are no abnormalities of the pancreas, intestine, or kidneys.
Which is the most likely cause of this patient's pain?

A. Diabetic autonomic neuropathy
B. Diabetic radiculopathy
C. Herpes zoster
D. Pancreatitis
E. Passed kidney stone

17.2. ANSWER: B) Diabetic radiculopathy

Diabetic neuropathy has myriad manifestations and is generally more common in patients with long disease duration and suboptimal glycemic control. Classification is subdivided into somatosensory, motor, and autonomic. The most common presentation involves damage to sensory nerve fibers and typically affects the distal extremities in a "stocking-glove" distribution

Affected patients describe numbness, paresthesias, and occasionally sharp, lancinating pains. Less common manifestations are acute sensory neuropathies characterized by sudden pain and dysesthesias in the distribution of one or more individual peripheral nerves or nerve roots. The patient in this vignette has left flank and left upper quadrant discomfort in the distribution of left nerve root T10. This may be seen in acute diabetic mononeuropathy or radiculitis (Answer B).

17.3. ANSWER: B) Diabetic radiculopathy

Autonomic dysfunction (Answer A) may affect one or several organ systems, including the vasculature (orthostatic hypotension), the heart (silent ischemia, abnormal cardiac rhythms), the gastrointestinal tract (gastroparesis, constipation, diarrhea from bacterial overgrowth), and the urinary bladder (atonic bladder, chronic urinary tract infections, overflow incontinence). It does not cause pain syndromes

Herpes zoster (Answer C) can cause localized pain in a pattern similar to the one described here, but it does not cause dramatic tenderness. However, the pain can precede the typical rash but not usually for 1 week. Pancreatitis (Answer D) is unlikely without more nausea and pain in relation to eating. In this patient, the normal amylase and lipase values and normal findings on CT also make pancreatitis unlikely.

17.4. ANSWER: B) Diabetic radiculopathy

Lastly, a small amount of blood in the urine is not uncommon in persons who have had diabetes for more than 10 years, especially if they have chronic kidney disease (as evidenced by proteinuria). While nephrolithiasis (Answer E) can produce flank pain and hematuria, it should be apparent on CT, and passing the stone would relieve most of the pain.

Educational Objective:

Diagnose rare syndromes of diabetic neuropathy.

18.1. A 52-year-old ♂ presents for evaluation of hypoglycemia. He has been experiencing frequent hyperadrenergic symptoms over the last six months, with a recent episode of confusion. Two weeks ago, he was taken to the emergency department following a syncopal event during which his blood glucose concentration was documented as 39 mg/dL (2.2 mmol/L). The neuroglycopenic episodes can occur when fasting or during the day, and his symptoms always improve with carbohydrate intake. He has gained 8 kg over the past 6 months. He does not use illicit drugs or drink alcohol. He is on pravastatin, pantoprazole, amlodipine, metoprolol, aspirin, biotin, cinnamon, chromium, and VD. He is in the process of divorcing and has been significantly stressed. Exam: BMI: 31. He has no other notable features. Lab: in ER 2 weeks ago: Plasma glucose 40 mg/dL (70-99 mg/dL). Plasma insulin 28 µIU/mL (1.4-14). Plasma C-peptide 3 ng/mL (0.5-2). TSH 1.2 mIU/L (0.5-5). Plasma proinsulin: 88.1 pg/mL (26.5-176.4). Plasma β-hydroxybutyrate: 1.2 mmol/L. Insulin antibodies: negative. eGFR 85 mL/min per 1.73 m^2 (>60). Based on this patient's history and test results, which is the best next management step?

A. Abdominal CT
B. Cosyntropin-stimulation test
C. IGF-2 measurement
D. Standard supervised 72-hour fast
E. Sulfonylurea screen

18.2. ANSWER: E) Sulfonylurea screen: This patient has severe hypoglycemia due to either an insulinoma or sulfonylurea intake. Before diagnosing insulinoma and pursuing localizing studies (Answer A), a sulfonylurea screen (Answer E) must be performed because sulfonylureas stimulate β cells to release insulin, C-peptide, and proinsulin; the hypoglycemia panel looks similar to that of insulinoma. Abdominal CT can be misleading in the absence of a definitive diagnosis and after sulfonylureas have been ruled out as a cause of hypoglycemia. The patient himself, his wife, or a pharmacy error could account for the sulfonylurea intake. A plasma insulin concentration of 3.0 µIU/mL or higher (220.8 pmol/L) by immunochemiluminometric assay, when the plasma glucose concentration is below 55 mg/dL (<3.1 mmol/L), indicates insulin excess and is consistent with hyperinsulinemia (either from insulinoma, exogenous insulin, or sulfonylurea).

18.3. ANSWER: E) Sulfonylurea screen: Plasma C-peptide distinguishes endogenous from exogenous hyperinsulinemia at a cutoff value of 0.6 ng/mL (0.20 nmol/L). In patients with insulinoma or sulfonylurea intake, the C-peptide concentration is at least 0.6 ng/mL (20.20 nmol/L), as opposed to exogenous insulin where the C-peptide concentration is 0.6 ng/mL (0.20 nmol/L). A plasma proinsulin concentration of 44 pg/mL or greater (25.0 pmol/L) is seen in the setting of insulinoma or sulfonylurea intake. Because of the antiketogenic effect of insulin, plasma α-hydroxybutyrate concentrations are lower in patients with insulinoma than in those without. All patients with hyperinsulinemia or IGF-mediated hypoglycemia have plasma α-hydroxybutyrate values of 2.7 mmol/L or less. A plasma sulfonylurea screen would reveal the sulfonylurea agent causing the hypoglycemia.

18.4. ANSWER: E) Sulfonylurea screen: In adrenal insufficiency, the plasma insulin concentration is less than 3.0 µIU/mL (<20.8 pmol/L), plasma C-peptide concentration is less than 0.6 ng/mL (<0.20 nmol/L), plasma proinsulin concentration is less than 44 pg/mL (<5 pmol/L), and plasma β-hydroxybutyrate concentration is greater than 2.7 mmol/L. Thus, there is no need for a cosyntropin-stimulation test (Answer B). In IGF-2-secreting tumors, the plasma insulin is less than 3.0 µIU/mL (<20.8 pmol/L), plasma C-peptide concentration is less than 0.6 ng/mL (<0.20 nmol/L), plasma proinsulin concentration is less than 44 pg/mL (<5 pmol/L), but plasma β-hydroxybutyrate concentration is 2.7 mmol/L or less. Thus, there is no need for IGF-2 measurement (Answer C). There is no role for a supervised fast (Answer D) in this case, as there is already documentation of all the laboratory tests needed during the episode of hypoglycemia in the emergency department.

Educational Objective:

Guide the appropriate evaluation of hypoglycemia.

19.1. A 37-year-old ♀ with T1D is attempting to become pregnant and is not using birth control with her partner. Recently, HbA1c fell from 10.3% to 6.5% (89 to 48 mmol/mol) with marked intensification of glycemic control. She has not seen an ophthalmologist for several years. Funduscopic examination documents the findings shown (see image).

In addition to seeing an ophthalmologist for a dilated eye exam, which is the best next step regarding her retinopathy, assuming she has developed macular edema?

A. Begin ranibizumab injections
B. Focal laser photocoagulation
C. Panretinal laser photocoagulation
D. Perform a vitrectomy

19.2. ANSWER: B) Focal laser photocoagulation

The image in the vignette shows extensive nonproliferative retinopathy, with retinal hemorrhages and hard exudates. Focal laser photocoagulation (Answer B) would target the macular edema and spare her vision. If she becomes pregnant, close follow-up would be required throughout her pregnancy.

Ranibizumab injections (Answer A) are not recommended for use in pregnancy due to a theoretical risk to the developing fetus. In a non-pregnant individual, ranibizumab is often the first choice. This patient could already be pregnant or is close to becoming pregnant, which would mean she should not receive antivascular endothelial growth factor (anti-VEGF) therapy.

Panretinal laser photocoagulation (Answer C) is not needed to treat this patient's nonproliferative retinopathy.

19.3. ANSWER: B) Focal laser photocoagulation: The Early Treatment of Diabetic Retinopathy Study examined the effect of treating eyes with mild nonproliferative diabetic retinopathy or early proliferative diabetic retinopathy to determine the best timing of photocoagulation. Rates of vision loss were low with either treatment applied early or delayed until the development of high-risk characteristics, namely disc neovascularization or vitreous hemorrhage with any retinal neovascularization. Because of this low rate and the risk of complications, the report suggests that scatter photocoagulation be deferred in eyes with mild-to-moderate nonproliferative diabetic retinopathy. As this patient does not have high-risk characteristics, scatter photocoagulation is not indicated now. Focal treatment is the best option for this patient's macular edema. Vitrectomy (Answer D) is reserved for eyes with hemorrhaging or scar tissue of the retina. She does not have either.

Educational Objective:

Recommend appropriate management of nonproliferative diabetic retinopathy and macular edema in a patient planning pregnancy.

20.1. A 20-year-old ♂ with a 3-year history of T1D never self-monitors his blood glucose and does not adjust his premeal insulin. HbA1c: 9.2% (77 mmol/mol), and it has never been lower than 8.8% (73 mmol/mol). He is beginning to be concerned about his risk for developing diabetes-related complications, especially blindness, and he wants to know if this can be prevented. Which is the adjusted mean risk reduction for developing retinopathy based on Diabetes Control and Complications Trial (DCCT) data for the intensively treated group?

A. 10%–25%
B. 25%–50%
C. 50%–70%
D. 70%–85%
E. >85%

20.2. ANSWER: D) 70%-85%

Vision loss from diabetes remains a major cause of blindness worldwide. Numerous epidemiological studies and clinical trials have documented the importance of glycemic control in patients with diabetes, including the Diabetes Control and Complications Trial (DCCT). Published in 1993, the DCCT was a landmark study that compared the effects of intensive versus conventional control on the onset and progression of diabetes-related complications over 6.5 years in more than 1400 patients with fairly early type 1 diabetes. The intensive control group showed a 76% reduction (Answer D) in the adjusted mean risk of developing retinopathy compared with the control group. Also documented was a 54% slowing of progression of mild established retinopathy and a 47% reduction in the development of proliferative or severe proliferative retinopathy. Furthermore, the occurrence of microalbuminuria was reduced by 39%, macroalbuminuria by 54%, and clinical Neuropathy by 60%

Educational Objective:

Counsel patients with type 1 diabetes regarding the magnitude of the potential impact of intensive control on the development of retinopathy.

REFERENCE(S)

Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986. PMID: 8366922

21

ANSWER: C) She has excessive

hyperglycemia

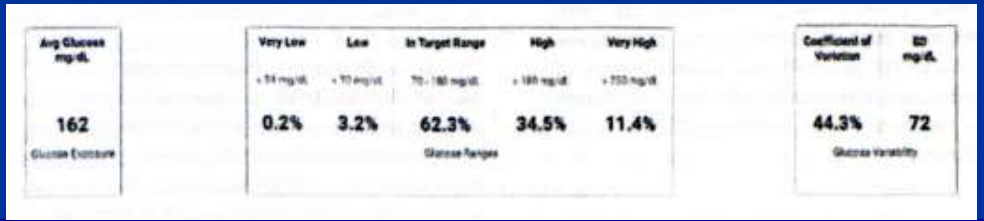
The current American Diabetes Association guidelines recommend the following for glycemic targets when continuous glucose monitoring is used in nonpregnant adults:

21.1. A 57-year-old ♀ 21 presents for management of T2D, which she has had for 16 years. She currently takes Metformin 1000 mg twice/day, and insulin glargine 20 U once/day. HbA1c: 6.7% (50 mmol/mol), and she has no signs or symptoms of hypoglycemia.

She is a professional violinist and has consistently declined glucose monitoring using fingerstick measurements.

Professional continuous glucose monitoring is recommended. She wears the device for 10 days, and the numerical results of her ambulatory glucose profile are shown (see image below). Which of the following is the correct interpretation of this patient's ambulatory glucose profile?

A. Her overall glycemic control meets recommended targets
B. She has acceptable glucose variability
C. She has excessive hyperglycemia
D. She has excessive hypoglycemia
E. The mean glucose value is consistent with her HbA1 value



21.2. ANSWER: C) She has excessive hyperglycemia

The current American Diabetes Association guidelines recommend the following for glycemic targets when continuous glucose monitoring is used in nonpregnant adults:

Time-in-range = >70%

Time-below-range = <4%

Time-below-range (54 mg/dL [<3.0 mmol/L]) = <1%

This patient's percentage of time-in-range is lower than the general time-in-range target because of excessive hyperglycemia (Answer C). The percentage of time she has hypoglycemia is acceptable (thus, Answer D is incorrect). Acceptable variability is considered to be below a coefficient of variation of 36% (thus, Answer B is incorrect). Her overall glycemic control does not meet recommended targets (thus, Answer A is incorrect).

21.3. ANSWER: C) She has excessive hyperglycemia

Empirical evidence from the AIC-Derived Average Glucose study showed that a HbA1c: 7% (53 mmol/mol) correlated approximately to a mean plasma glucose concentration of 155 mg/dL (8.6 mmol/L), and a HbA1c 6% (42 mmol/mol) correlated to a mean plasma glucose of 126 mg/dL (7 mmol/L). Therefore, this patient's hemoglobin Ate should produce a mean glucose value well < 162 mg/dL (< 9 mmol/L) (thus, Answer E is incorrect). She has polycythemia, typically requiring intermittent phlebotomy. As this therapy is expected to increase.

Red blood cell turnover, hemoglobin A_1, is unlikely to provide an accurate and/or precise assessment of average blood glucose for the expected 60-90 days. For this reason, as clearly demonstrated in this patient's case, either frequent blood glucose monitoring or a continuous glucose monitoring profile has considerable potential for optimizing glycemic management.

Educational Objective:

Select appropriate premeal glucose targets for managing type 2 diabetes.

22.1. A 47-year-old ♂ with a 25-year history of T1D with retinopathy has been admitted to the hospital after presenting with an isolated concern of new-onset double vision and feeling unsteady when walking since this morning. He notes occasional blurry vision after large meals, some tingling in his feet, and decreased libido. He has no symptoms suggestive of thyroid disease or adrenal insufficiency. Neuro Exam: he is awake, responsive, and oriented to person, place, and time. His right eye is deviated "down and out." Left eye movements are normal. The rest of the cranial nerves are intact. There is no ptosis or nystagmus, and pupils are equal and reactive to light. He has mild reduction of sensation bilaterally in the feet. Lab: (at admission): Blood glucose: 203 mg/dL (70-99). HbA1c: 8.5% (4-5.6%) (69 mmol/mol). Head CT reveals no evidence of hemorrhage or Infarct but shows an enhancing suprasellar mass involving the superior pituitary stalk. MRI with sellar and suprasellar cuts confirms the presence of a pituitary mass with suprasellar extension, but it does not show evidence of optic or oculomotor nerve impingement. Diplopia is still present on the third hospital day Which is the most likely explanation for his diplopia?

A. Macular edema
B. Mononeuritis affecting the third cranial nerve
C. Pituitary macroadenoma
D. Reversible ischemic neurologic deficit
E. Unilateral endocrine ophthalmopathy

22.2. ANSWER: B) Mononeuritis affecting the third cranial nerve

In oculomotor (third) nerve palsy, the eye involved is deviated "down and out" (i.e., infraducted and abducted). Diabetic mononeuropathy (Answer B) is one of the less common forms of neuropathy. Patients with diabetes can develop diplopia from isolated oculomotor (third), trochlear (fourth), or abducens (sixth) nerve palsies. Ophthalmoplegia, despite being a rare entity in diabetes, is associated with anxiety for the patient and is a diagnosis made after other pathologies have been ruled out. In a 10-year series of more than 6,000 patients hospitalized with diabetes, 0.4% were diagnosed with ophthalmoplegia, among whom isolated third nerve palsies accounted for the most (59.3%), with sixth nerve palsies and multiple palsies accounting for the remainder. The mean age in this series was 65 ± 10 years, the mean duration of diabetes was 16 ± 10 years, and most patients had T2D

22.3. ANSWER: B) Mononeuritis affecting the third cranial nerve

Most had suboptimally controlled diabetes with a mean hemoglobin A level of 8.8% ± 2.5% (73 ± 3 mmol/mol). Those with sixth nerve palsies had higher rates of coexisting diabetic retinopathy and cardiovascular disease risk factors. Among all cases of ocular misalignment from cranial nerve palsies, third nerve palsies are important because a subset is caused by life-threatening aneurysms. In a recent series of 145 patients from the Rochester Epidemiology Project, the most common causes of acquired third nerve palsy were presumed microvascular (42%), trauma (12%), compression from neoplasm (11%), post-neurosurgery (10%), and compression from aneurysm (6%). No specific treatment has been established for nerve palsy-induced diplopia in patients with diabetes. Management is expected, and the patient should be reassured. Unilateral endocrine ophthalmopathy (Answer E) with entrapment of ocular muscles can cause diplopia, but its onset is not expected to be sudden, and other features such as proptosis, chemosis, and conjunctival injection are common accompaniments.

22.4. ANSWER: B) Mononeuritis affecting the third cranial nerve

In addition, a characteristic appearance of the extraocular muscles on CT (enlargement of the extraocular muscle bellies with sparing of their tendinous insertions [frequently: inferior rectus > medial rectus > superior rectus]) associated with endocrine ophthalmopathy was not seen in this patient. Pituitary adenomas (Answer C) do not typically cause isolated third nerve impingement. As these neoplasms grow, they are more likely to cause visual field defects due to pressure on the optic nerve, rather than impinging the oculomotor nerves. This patient does not have loss of vision due to optic nerve compression, just isolated third cranial nerve oculomotor deficits. By definition, he does not have a reversible ischemic neurologic deficit (Answer D) as an etiology for his oculomotor palsy because the deficit is still persistent after several days. Macular edema (Answer A) would not be expected to cause diplopia.

Educational Objective:

Diagnose third cranial nerve palsy.

23.1. A 25-year-old ♂ with a 2-year history of T1D has recently started to play tennis and is preparing for a 1-hour tennis game to be played at 8 a.m. The last time he played, he had a severe hypoglycemic episode that required his friend to assist him with finding his glucose tablets. His usual regimen is insulin glargine, 14 units every morning, and rapid-acting insulin with an insulin-to-carbohydrate ratio of 1:10 for meals. He eats breakfast at 7 a.m. His most recent hemoglobin A value is 6.7% (50 mmol/mol). He asks for advice about his insulin regimen the morning of the tennis game, assuming on that day his fasting glucose is in the usual range of 120-140 mg/dL (6.7-7.8 mmol/L).

Which is the best recommendation?

A. Eat breakfast, take insulin glargine (14 units) and insulin lispro with an insulin-to-carbohydrate ratio of 1:20
B. Eat breakfast, take insulin lispro with an insulin-to-carbohydrate ratio of 1:10 and delay the glargine dose until the evening
C. Eat breakfast, take insulin lispro with an insulin-to-carbohydrate ratio of 1:10 and lower the glargine dose to 7 U
D. Skip breakfast and insulin lispro; drink 8 oz of orange juice before the game

23.2. ANSWER: A) Eat breakfast, take insulin glargine (14 units) and insulin lispro with an insulin-to-carbohydrate ratio of 1:20

With an adequate concentration of insulin on board, aerobic activities are associated with reductions in blood glucose concentrations. In contrast, anaerobic activities usually do not reduce blood glucose concentrations and may be associated with glucose elevations in certain circumstances. Aerobic exercise is associated with a more modest rise (2- to 4-fold) in catecholamines, while anaerobic exercise is associated with a much higher increase in catecholamine release (14- to 18-fold rise). It is also well established that exercise increases muscle glucose uptake through insulin-dependent and insulin-independent mechanisms. Glycemia during exercise is also affected by substrate availability, as well as insulin concentrations. The net balance effect varies among individuals.

23.2. ANSWER: A) However, in general, assuming insulin is present and the blood glucose level is within the normal range, aerobic activity can lead to hypoglycemia, usually during or immediately after exercise, although in some patients, delayed hypoglycemia hours after exercise can occur. In the presented scenario, the best way to prevent hypoglycemia is to cut back on the mealtime bolus by 50%, just an hour before playing tennis (Answer A). Skipping lispro insulin entirely and drinking a high-glycemic index beverage (Answer D) is not recommended because the insulin-deficient state is likely to lead to post-exercise hyperglycemia Taking the full bolus at breakfast but reducing the basal dose (Answer C) would most likely lead to hypoglycemia during exercise and to hyperglycemia later in the day. Delaying the 24h basal insulin for 12 hours (Answer B) would lead to late hyperglycemia and possibly diabetic ketoacidosis due to an insulin-deficient state.

Educational Objective: Manage insulin therapy during exercise.

24.1. A 29-year-old ♀ presents for management of uncontrolled diabetes. Diabetes was diagnosed two years ago, but she has never had optimal glycemic control. She was unable to tolerate Metformin due to gastrointestinal adverse effects. She briefly took an SGLT-2 inhibitor, but she had recurrent yeast infections, so she stopped this therapy. Glimepiride was not effective. Six weeks ago, she began taking Dulaglutide, 1.5 mg, once-weekly, and her Glucose values have not decreased significantly since this regimen change. Graves' disease was recently diagnosed and is being managed with methimazole. She has been overweight since she was a teenager. She restricts her calories and exercises almost every day. She has been losing weight, but she has also been hyperthyroid. Her fasting and 2-hour postprandial glucose 180-220 mg/dL. She has never had diabetic ketoacidosis. She has a family history of T2D. Exam: weight 109 kg. BMI: 34. BP: 132/88. Pulse: 108. There is no exophthalmos. The thyroid gland is uniformly enlarged. She has no acanthosis nigricans. The rest of the examination Findings are normal. HbA1c: 10.8% (95 mmol/mol). Which should be measured to help decide the next step in improving this patient's diabetes management?

A. C-peptide
B. Fasting insulin
C. Fructosamine
D. Glutamic acid decarboxylase antibodies

24.2. ANSWER: D) Glutamic acid decarboxylase antibody

This woman with obesity has diabetes that has been unresponsive to a variety of medications typically used to treat type 2 diabetes. Glutamic acid decarboxylase antibodies (Answer D) were measured based on her clinical presentation to assess for the presence of autoantibody-associated diabetes of the adult, and the result confirmed the diagnosis. Latent autoimmune diabetes in adults (LADA) is an autoimmune form of diabetes defined by age at onset older than 30 years, presence of diabetes-associated autoantibodies, and no insulin treatment requirement for a period after diagnosis (as has been the case in this patient). The three criteria conventionally used to define LADA are nonspecific: namely, age at diagnosis, autoantibody positivity, and need for insulin treatment. Metabolic changes at diagnosis of LADA reflect a broad clinical phenotype ranging from DKA to mild non-insulin-requiring diabetes.

24.3. ANSWER: D) Glutamic acid decarboxylase antibody

The latter phenotype is the most prevalent form of adult-onset autoimmune diabetes and is probably the most prevalent form of autoimmune diabetes in general. Patients with adult-onset autoimmune diabetes have less HLA-associated genetic risk and fewer diabetes-associated autoantibodies compared with patients with childhood-onset type 1 diabetes. Although LADA is associated with the same genetic and immunologic features as classic autoimmune type 1 diabetes, it also shares some genetic features with type 2 diabetes, which raises the question of genetic heterogeneity predisposing to this form of the disease. The potential value of screening patients with adult-onset diabetes for diabetes-associated autoantibodies to identify those with LADA is emphasized by their lack of clinically distinct features, their different natural history compared with T2D, and their potential need for a dedicated management strategy.

24.4. ANSWER: D) Glutamic acid decarboxylase antibody

Diabetes-associated autoantibodies include autoantibodies to glutamic acid decarboxylase, insulinoma-associated antigen IA-2, islet cells, and zinc transporter 8 (ZnT8A). The definition of autoantibody positivity is not unequivocal, and different cut-off points have been applied in different studies. Longitudinal studies observe changing autoantibody status over time, and even though most patients are positive for only one type of autoantibody, existing autoantibodies may be lost and other autoantibodies may develop. This woman's blood glucose values are consistent with her hemoglobin A level, so there is no reason to do alternative testing to confirm her current level of glycemic control. Fructosamine measurement (Answer C) would therefore not contribute to her management. Fasting insulin levels (Answer B) are used to assess the degree of insulin resistance, which is not a consideration in this patient right now.

24.5. ANSWER: D) Glutamic acid decarboxylase antibody

Finally, adults with LADA are more likely to have lower C-peptide levels than those without diabetes-associated autoantibodies, but because both cohorts may still make C-peptide, its measurement (Answer A) is not useful in distinguishing between the two conditions. This patient's glutamic acid decarboxylase antibody level was 9832 IU/mL (normal, < 5 IU/mL), which confirms a diagnosis of LADA. Islet-cell antibodies were undetectable (which was somewhat unanticipated). She is now on basal-bolus insulin therapy and is learning about carbohydrate counting, insulin-to-carbohydrate ratios, and sick-day rules for insulin management to prevent diabetic ketoacidosis in the event of an intercurrent illness. She is no longer taking dulaglutide, and her glycemic control is markedly improved.

Educational Objective:

Diagnose latent autoimmune diabetes in adults.

25.1. A 25-year-old ♂ with T1D is found vomiting and disoriented after attending a party with his friends. He moved out of his family's home four months ago to live on his own. He manages his diabetes with multiple daily insulin injections. Five months ago, HbA1c 6.9% (52 mmol/mol). His roommate calls the paramedics who transport him to the emergency department. In the emergency department, he appears somewhat confused and lethargic. He admits to having consumed an unusual amount of cannabis, as well as two beers, that evening. He describes vaping cannabis frequently since moving away from home. He recalls giving himself insulin earlier in the day.

Exam: he is afebrile. BP: 110/72. Pulse: 90. Respiration: 30.

Lab: Glucose 280 mg/dL. Na: 146 mg/dL (136-142). Bicarbonate 18 mEq/L (21-28). β-Hydroxybutyrate: 2.1 mmol/L. HbA1c: 7.1% (4-5.6%) (54 mmol/mol). pH = 7.45 (7.35-7.45). Urea: 34 mg/dL (8-23). Cr: 1.4 mg/dL (0.7-1.3). K: 5 mEq/L (3.5-5). Urinalysis: 4+ glucose, large ketones, few white blood cells, no red blood cells.

Which most likely precipitated his condition?

A. Adrenal insufficiency
B. Alcohol intoxication
C. Cannabis
D. Infection
E. Insulin rationing

25.2. ANSWER: C) Cannabis: Cannabis use (Answer C) has been shown to cause an unusual form of diabetic ketoacidosis, with a more alkalotic pH. These individuals tend to have vomiting before they are ketotic, and symptoms may be due to hyperemesis caused by the cannabis. This causes ketosis followed by hyperglycemia. He is not hypotensive or hypoglycemic, so he does not likely have adrenal insufficiency (Answer A). He has no evidence of infection (Answer D). While alcohol intoxication (Answer B) is also an important consideration, typically in this setting the glucose level is low due to suppression of gluconeogenesis. Insulin rationing (Answer E) can occur if patients lack access to medical care/health insurance, but this patient seems to be continuing to administer insulin and take care of his diabetes, even though he has moved away from home.

Educational Objective:

Identify features of cannabis-mediated diabetic ketoacidosis

26.1. A 31-year-old woman with a history of type 1 diabetes since age 2 and Hashimoto's thyroiditis is concerned about the sudden onset of a rash on her upper extremities. It started at 8:30 AM, at which point her hands became swollen, red, painful, and burning with a pruritic rash covering both of her arms (see image, following page). She had not yet administered her morning insulin injection. She had a similar episode 2 years ago. At that time, her physician changed her brands of insulin and the type of thyroid hormone replacement. The lesions resolved over the course of 3 months with symptomatic improvement with cetirizine HCl and diphenhydramine. She has never experienced redness before or itching at insulin injection sites. She has not changed her usual soaps, lotions, or laundry detergent. She has a house cat that is on flea prevention therapy.

Which is the diabetes-associated cause of the patient's pruritic skin condition?

A. Chronic autoimmune urticaria
B. Hypersensitivity reaction to flea bites
C. Insulin allergy
D. Necrobiosis lipoidica
E. Perforating collagenosis

26.2. ANSWER: A) Chronic autoimmune urticaria

Chronic autoimmune urticaria (Answer A) is a syndrome that occurs at an increased frequency in patients with autoimmune disorders. Type 1 diabetes and Hashimoto's thyroiditis are commonly associated with this condition. In general, chronic autoimmune urticaria is treated symptomatically, but in severe cases, omalizumab has been used. The etiology is thought to be due to autoantibodies to the IgE receptors. Flea bites (Answer B) are unlikely given the rash's location and appearance. Flea bites are a consideration in the differential diagnosis of scattered pruritic lesions, but this would not be specifically associated with diabetes. Necrobiosis lipoidica (Answer D) is a rare, chronic, granulomatous skin disorder that affects 0.3% of patients with diabetes. The skin lesions are characterized by thinning of the skin, dilated capillaries, and lipid deposits.

26.3. ANSWER: A) Chronic autoimmune urticaria

. This appearance is quite different from the lesions seen in this case. While the etiology and pathogenesis of necrobiosis lipoidica are still controversial, it is thought that microangiopathy plays an important role. The legs are the most common site for necrobiosis lipoidica, but involvement of other areas such as the abdomen, upper extremities, and scalp has been described. Benefit has been reported from different Treatment regimens such as corticosteroid therapy (topical, intralesional, and systemic), enhancers of wound healing, surgery, and immunomodulating therapies (including photochemotherapy).
While perforating collagenosis (Answer E) is more common in persons with diabetes, it is not a diffuse process as seen in the photograph in this vignette.

26.4. ANSWER: A) Chronic autoimmune urticaria

Perforating collagenosis presents as hyperkeratotic papules with transepidermal elimination of degenerated material, including collagen or elastic fibers. It is generally diagnosed with a biopsy. This condition may be difficult to treat, but it often responds to light therapy. Insulin allergy (Answer C) is unlikely due to the location of the lesions and the timing of the reaction. If it were an insulin allergy, the lesions would start as a localized reaction at the injection site. Before the introduction of recombinant human insulin to the market in the early 1980s, insulin allergy was a common occurrence. Allergy to human insulin preparations, although rare, still occurs When insulin allergy is suspected, it is important to rule out causes such as allergies to inactive ingredients in the insulin formulation (e.g., protamine sulfate, zinc, and metacresol) and allergies to latex or alcohol swabs used in the insulin preparation and injection process.

26.5. ANSWER: A) Chronic autoimmune urticaria

Allergies to inactive ingredients in the insulin formulation can often be resolved by switching to a different type of insulin that does not contain the responsible inactive ingredient. In rare cases, an individual can be allergic to the insulin molecule itself. Insulin allergy may present as a localized reaction at the injection site or a more severe, generalized reaction that can range from urticaria to anaphylaxis.

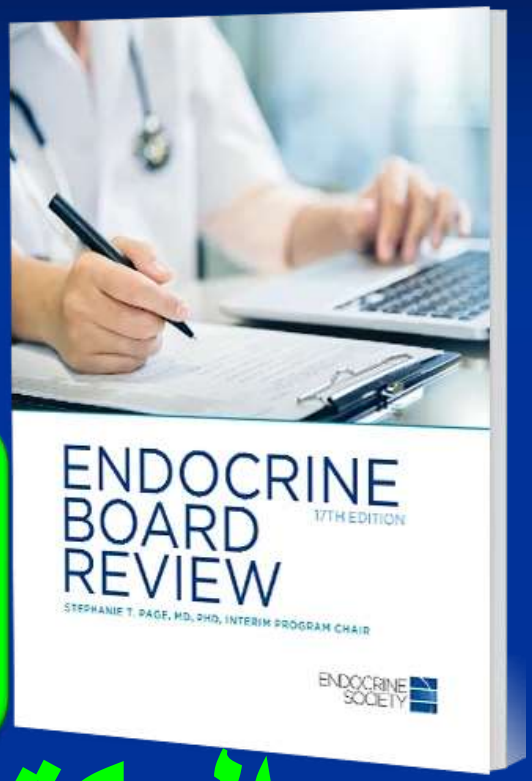
Educational Objective:

Differentiate among specific skin disorders associated with diabetes

مراجعات البورد في الغدد

EBR.17

Diabetes 2



الدكتور محمد الشعباني

1.2. ANSWER: C) "Ga DOTA-somatostatin analogue PET

This patient appears to have either a localized or metastatic pancreatic neuroendocrine tumor (PNET). It is also possible he has a multifocal nonmetastatic PNET that was not identified on CT. With his remote history of colorectal cancer, characterizing the liver lesions is required to arrive at the appropriate next step in management. In the case of a possible metastatic PNET, the best next step is to use an imaging modality that has a high detection rate for metastatic lesions. The current standard imaging approach in this case is to identify a specific hormone receptor-targeted radiolabeled ligand that can be used along with a usual body imaging modality (e.g., PET or CT) to both identify and help characterize multiple lesions While GLP-1 receptors are overexpressed in > 90% of localized insulinomas, this is the case in < 40% of metastatic lesions outside the pancreas, making radiolabeled GLP-1 receptor ligands, such as exendin-4 (Answer D), less sensitive for diagnosis.

1.3. ANSWER: C) "Ga DOTA-somatostatin analogue PET

Hence, in the case of possible metastatic insulinoma, the somatostatin analogue DOTATATE (Answer C) is considered a superior imaging radioligand. Although not the reason for the correct answer, it is also important to note that exendin-4 is not readily available in many areas of the world, including most medical centers in the United States. Genetic testing for pathogenic variants in RET (Answer B), which is typically included in a gene panel, may eventually be appropriate in the diagnostic pathway of this patient's malignancy. However, RET is not as closely associated with insulinoma as other genes, such as MENI, VHL, and NF1. Moreover, genetic testing at this stage would not help to clarify whether the insulinoma is localized, multifocal, or metastatic.

1.4. ANSWER: C) "Ga DOTA-somatostatin analogue PET

MRI would not provide much additional characterization, and T2 hyperintensity (not T1 [Answer E]) would be expected. Calcium stimulation (Answer A) is indicated in the case of multifocal lesions in the pancreas to identify the predominant anatomical origin of insulin hypersecretion. Since this patient has only 1 clearly identified pancreatic lesion, this would not be appropriate.

Educational Objective:

Select the correct imaging modality in the setting of a possible metastatic pancreatic neuroendocrine tumor.

2.1. A 63-year-old ♀ with a 23-year history of T2D presents for routine follow-up. Diabetes was initially diagnosed during pregnancy complicated by preeclampsia, and over time she developed hypertension and hyperlipidemia. Twelve years ago, she had a myocardial infarction requiring a two-vessel stent. She does not smoke cigarettes

Medications: Aspirin 81 mg/day; Losartan: 100 mg/day; Metoprolol: 50 mg/day; Rosuvastatin 40 mg/day; and Semaglutide 2 mg once/week. She stopped taking metformin 6 months ago because of diarrhea.

Exam: she appears well. BP: 136/88. Pulse: 88. Lungs are clear to auscultation. CV exam reveals mild pedal edema and diminished dorsalis pedis pulses bilaterally (noted on past examinations).

Lab: HbA1c: 7.4% (4-5.6%) (57 mmol/mol). Hematocrit: 38% (35-45%). LDL: 48 mg/dL (<100). Cr: 1.1 mg/dL (0.6-1.1). Urinary alb/Cr 25 mg/g. mg/Cr. TSH 0.75 ml (0.5-5). Terminal pro B-type natriuretic peptide: 204 pg n

Which should be recommended as the best nest therapy specialty?

A. Add dapagliflozin, 5 mg daily
B. Add Metformin extended-release, 500 mg daily
C. Add Pioglitazone, 20 mg daily
D. Reduce Rosuvastatin dosage to 20 mg daily
E. Stop Semaglutide and add Tirzepatide, 2.5 mg weekly

2.2. ANSWER: A) Add dapagliflozin, 5 mg daily

This patient has longstanding diabetes and a history of preeclampsia, both strong risk factors underlying her atherosclerotic heart disease and potential development of ischemic cardiomyopathy. Based on the N-terminal pro-B-type natriuretic peptide value higher than 125 pg/mL and in light of her physical exam, she may have either stage A or B heart failure. Of the presented options, dapagliflozin (Answer A) has the best potential to achieve both goals of modestly improving glycemic control (expected to lower hemoglobin A_1 by approximately 0.5% in those with a glomerular The filtration rate is >45 mL/min per 1.73 m^2) and improving outcomes related to congestive heart failure. It is also important at this stage to proceed with characterizing her congestive heart failure. Thus, referring her to a cardiologist and arranging an echocardiogram are both sensible next steps.

2.3. ANSWER: A) Add dapagliflozin, 5 mg daily

People with diabetes are at higher risk for developing heart failure, as shown in multiple longitudinal, observational studies. This association is seen in both type 1 and type 2 diabetes. Patients with diabetes are particularly vulnerable to progressing from early, asymptomatic stages of heart failure (stages A and B) to more severe symptomatic stages (stages C and D). Early detection, risk assessment, and treatment of risk factors in these patients can help prevent the progression to symptomatic heart failure. Numerous observational studies have demonstrated that measuring natriuretic peptides, such as B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), can identify individuals at risk of heart failure and its complications, including mortality. Given these findings and the lack of a validated heart failure risk score, the American Diabetes Association currently recommends screening any adult with type 2 diabetes for heart failure by measuring a natriuretic peptide.

2.4. ANSWER: A) Add dapagliflozin, 5 mg daily

The biomarker threshold for abnormal values is 50 pg/mL for BNP and 125 pg/mL for NT-proBNP. Importantly, natriuretic peptides can be elevated secondary to several conditions, including kidney insufficiency, pulmonary disease (including pulmonary hypertension and chronic obstructive lung disease), obstructive sleep apnea, ischemic and hemorrhagic stroke, and anemia. Conversely, natriuretic peptide levels may be lower in persons with obesity and must be interpreted carefully. Although the thiazolidinedione pioglitazone (Answer C) is included among cardioprotective agents in guidance statements (e.g., the American Diabetes Association's Standards of Medical Care for Diabetes), all guidelines warn of pioglitazone's potential to exacerbate underlying congestive heart failure, regardless of whether it has already been diagnosed or is subclinical.

2.5. ANSWER: A) Add dapagliflozin, 5 mg daily

In the presence of Elevated BNP and this patient's history; prescribing pioglitazone is incorrect. While metformin may be better tolerated in the extended-release formulation (Answer B), and it is also potent enough to achieve its hemoglobin A target, it does not offer other benefits and the patient would be at risk of recurrent diarrhea. Switching semaglutide to tirzepatide (Answer E) may allow for increased potency over time. However, based on best-practice expert opinion publications, semaglutide (2 mg weekly) is expected to be more effective than tirzepatide (2.5 mg weekly [starting dosage]). Thus, it is unclear whether this switch to tirzepatide would result in improved glycemic control. Currently, two randomized controlled trials have been published that prove the benefit of semaglutide in individuals with cardiovascular disease and heart failure. This benefit is not yet formally established with tirzepatide.

2.6. ANSWER: A) Add dapagliflozin, 5 mg daily

Statin therapy has been associated with an increased onset of type 2 diabetes in those with prediabetes. However, the patient's current LDL-cholesterol concentration is consistent with current guidelines for patients with established atherosclerotic cardiovascular disease, and there is no evidence that reducing the statin dosage (Answer D) would improve her hemoglobin A_1 level.

Educational Objective:

Diagnose subclinical heart failure in people with longstanding diabetes and choose appropriate therapies.

3.1. A 54-year-old woman with a 5-year history of type 2 diabetes, hypertension, and hyperlipidemia presents for evaluation of diabetes management. Six months ago, she discontinued atorvastatin due to elevated liver enzymes. Two months ago, her primary provider advised her to stop metformin, but the transaminitis persisted. Before stopping metformin, HbA1c: 6.9% (52 mmol/mol).

Exam: she appears well. BP: 142/84. BMI 34. Mild 1+ pitting edema is noted bilaterally at the ankles. Medications: Metoprolol XR 100 mg/day; Lisinopril 10 mg/day; Ezetimibe 10 mg/day; and Apixaban 5 mg twice/day.

Lab: Cr 1.2 mg/dL (0.6-1.1). Glucose 180 mg/dL. Tg: 320 mg/dL (<150). AST: 51 U/L (20-48). ALT: 65 U/L (10-40). INR: 1. Platelet count: 151 × 10^{-10}/µL (150-450 × 10^{-10}/µL). The calculated Fibrosis-4 (FIB-4) score is 2.22 (low risk <1.3, intermediate risk 1.3–2.67; high risk >2.67).

Which of the following is the best next step in this patient's evaluation?

A. Hepatic ultrasonography
B. Liver biopsy
C. Liver MRI
D. Plasma albumin measurement
E. Vibration-controlled transient elastography

3.2. NSWER: E) Vibration-controlled 3 transient elastography

Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a range of liver conditions, ranging from simple macrovesicular hepatic steatosis (with or without mild inflammation) to metabolic steatohepatitis (MASH) and cirrhosis, occurring in the absence of significant alcohol consumption or other secondary causes of fatty liver disease. Significant alcohol consumption is defined as more than 21 standard drinks per week for men and more than 14 standard drinks per week for women over the 2 years preceding the evaluation. Recent research in adults indicates that MASLD affects more than 70% of individuals with type 2 diabetes, with approximately half of these cases progressing to MASH. Additionally, MASH substantially increases the already heightened cancer risk associated with diabetes and obesity.

3.3. NSWER: E) Vibration-controlled 3 transient elastography

Studies have shown that transaminitis alone is not a reliable marker for diagnosing MASLD, and abdominal imaging by itself is insufficient. Therefore, in this case, the Fibrosis-4 (FIB-4) index was appropriately used as an initial cost-effective tool to assess the likelihood of advanced MASLD. The patient's result fell within the indeterminate range. The FIB-4 index estimates the risk of hepatic fibrosis by incorporating age, plasma aminotransferase levels (AST and ALT), and platelet count. A value below 1.3 suggests a lower risk (fibrosis stage 0 or 1), while a value above 2.67 strongly indicates advanced fibrosis (stage 4). FIB-4 has good specificity but low sensitivity; hence, a negative result rules out fibrosis, but a positive result requires additional confirmatory testing. When results fall in the indeterminate category, as seen in this case, further noninvasive evaluation is necessary.

3.4. NSWER: E) Vibration-controlled 3 transient elastography

Such as elastography (Answer E), is recommended to assess liver stiffness. Hepatic ultrasonography (Answer A) lacks adequate specificity for quantifying and staging steatosis and fibrosis.

Liver MRI (Answer C) and liver biopsy (Answer B) may be considered to better characterize and/or confirm the results of elastography, but neither is recommended as a first-line diagnostic test.

Plasma albumin measurement (Answer D) as a surrogate marker of hepatic synthetic function lacks both sensitivity and specificity for steatohepatitis at any stage.

Educational Objective:

Choose the appropriate next test following documentation of an intermediate FIB-4 score for metabolic dysfunction-associated steatotic liver disease.

4.1. A 28-year-old pregnant ♀, currently at 14 weeks gestation, presents for evaluation of hyperglycemia. She has a known diagnosis of glucokinase (GCK)-related maturity-onset diabetes of the young (MODY), confirmed by genetic testing. After discussing the potential risks and benefits of chorionic villus sampling or amniocentesis for prenatal genetic testing, she declines. Her prepregnancy HbA1c: 6.2% (44 mmol/mol). Recent home glucose monitoring shows fasting glucose between 98-112 mg/dL (5.4 and 6.2 mmol/L) and postprandial glucose: 120-152 mg/dL (6.7-8.4 mmol/L). The fetal assessment at her 12-week US was appropriate for her gestational age. Which is the most appropriate management of her diabetes?

A. Initiate Glyburide if fasting glucose exceeds 126 mg/dL (>7 mmol/L)
B. Initiate Metformin therapy now to reduce maternal glucose levels
C. Start insulin if fetal growth exceeds 75th percentile on ultrasound
D. Start insulin now to maintain fasting glucose <95 mg/dL (<5.3 mmol/L) and postprandial glucose <140 mg/dL (<7.8 mmol/L)
E. Start insulin whenever fasting glucose >140 mg/dL (>7.8 mmol/L)

4.2. ANSWER: C) Start insulin therapy if fetal growth exceeds the 75th percentile on ultrasonography

GCK-related maturity-onset diabetes of the young (MODY) is caused by heterozygous pathogenic variants in the glucokinase gene (GCK), leading to a higher glucose threshold for insulin secretion. Patients with GCK-related MODY typically have mild fasting hyperglycemia (glucose, 100–130 mg/dL [5.6–7.2 mmol/L]) that does not lead to complications outside of pregnancy. During pregnancy, however, fetal growth is determined by whether the fetus inherits the GCK pathogenic variant. If the fetus inherits the pathogenic variant (affected), the fetus has the same higher glucose set point, and maternal hyperglycemia does not drive excessive growth. Conversely, if the fetus does not inherit the pathogenic variant (unaffected), maternal glucose levels may be relatively higher for the fetus, leading to macrosomia.

4.3. ANSWER: C) Current guidance derived from expert opinion indicates that in pregnant women with GCK-related MODY, insulin therapy should be deferred until fetal growth is assessed by means of ultrasonography, beginning in the late second trimester. This is partly driven by several case series indicating that standard maternal treatment does not alter the risk of macrosomia in unaffected neonates, but it does increase the risk of restricted growth in affected neonates. Thus, applying standard glucose targets in pregnancy (Answer D) is incorrect. Whenever there is evidence of fetal overgrowth, typically by an estimated fetal weight or abdominal circumference greater than 70% to 75%, the fetus is presumed to be unaffected by GCK-related MODY, and maternal insulin therapy is initiated. Thus, insulin therapy should be started if fetal growth exceeds the 75th percentile on ultrasonography (Answer C).

4.4. ANSWER: C) Some experts have reported a strategy of treating hyperglycemia from early in pregnancy using modified glycemic targets that are less stringent than the targets typically used during pregnancy but are derived from previous studies showing the relationship between maternal blood glucose and macrosomia. This strategy attempts to balance the risk of growth restriction in an affected fetus with the potential benefit of glucose-lowering therapy for an unaffected fetus. Such reported thresholds include fasting glucose values between 110 and 120 mg/dL (6.1–6.7 mmol/L). A fasting glucose value of 140 mg/dL (7.8 mmol/L) (Answer E), however, is significantly higher than these established thresholds, and, if applied, it would not be expected to reduce the risk of macrosomia in an unaffected fetus. There is no evidence that other therapies (e.g., glyburide [Answer A] or metformin [Answer B]) offer more or less benefit than insulin in pregnancies affected by GCK-related MODY.

Educational Objective: Apply a fetal growth-driven approach to managing GCK-related maturity-onset diabetes of the young (MODY) in pregnancy.

5.1. A 30-year-old ♀ presents at 11 weeks' gestation for diabetes management. T1D was diagnosed at age 24 in the setting of symptomatic polyuria, and she has since managed her diabetes with an automated insulin delivery pump integrated with continuous glucose monitoring. The insulin pump download reveals the following data:
Time-in-range (for pregnancy, 63-140 mg/dL [3.5-7.8 mmol/L]): 78%
Total insulin requirement: 14 U (0.2 U/kg/day); 70% delivered as nutritional, and 30% as basal
Insulin delivery is automatically suspended overnight most nights for up to 8 hours, often following a glucose value <70 mg/dL (<3.9 mmol/L) without a subsequent rise
She has checked her fingerstick glucose concentrations: twice/day and has found most values within 15 mg/dL (0.83 mmol/L) or 5-10% of the continuous glucose monitor's readings. She reports a strong family history of both T1D and T2D. Her father has T2D diagnosed at age 32 years that is managed with a Sulfonylurea and Metformin. His diabetes is complicated by chronic kidney disease. Her paternal aunt has T1D complicated by neuropathy, and she is treated with multiple daily doses of insulin. Her sister has type 1 diabetes, also managed with insulin pump therapy. Exam: BP: 116/76. Pulse: 78. Weight: 62 kg. BMI: 23. She appears well overall. Lab: basic metabolic panel and liver function tests: normal
Which is the most likely primary cause of diabetes in this patient?

A. A3243G pathogenic variant in mitochondrial DNA
B. Autoimmune destruction of β-islet cells
C. Congenital reduced pancreatic mass
D. Pathogenic variant in the glucokinase gene (GCK)
E. Pathogenic variant in the HNFI homeobox A gene (HNFIA)

5.2. ANSWER: E) Pathogenic variant in the HNF1 homeobox A gene (HNFIA): The patient in this vignette most likely has monogenic diabetes, often called maturity-onset diabetes of the young (MODY), characterized by (1) young age at diagnosis (often <25 years); (2) a marked family history of diabetes in every generation due to autosomal dominant inheritance; (3) absence of obesity and signs of insulin resistance; and (4) commonly mild hyperglycemia either without evidence of insulin requirement or very low insulin requirement. Monogenic forms of diabetes comprise a heterogeneous group of disorders. They are caused by single-gene pathogenic variants and are characterized by impaired insulin secretion. Up to 5% of all diabetes cases are monogenic, and affected patients are often undiagnosed or are misclassified as having type 1 or type 2 diabetes

5.3. ANSWER: E) Many pathogenic variants have been identified that cause diabetes by disturbing the coupling of blood glucose concentration and insulin secretion. The diagnosis can be confirmed by genetic testing where available. The specific feature in this case of a predominant prandial insulin requirement is Highly consistent with a pathogenic variant in the HNF1 homeobox A gene (HNFIA) (Answer E) on chromosome 12, commonly referred to as MODY type 3. While the diagnosis may not be critical during pregnancy, as insulin therapy is the most standard approach to care, the diagnosis should be considered to support other management options. Almost 70% of patients previously treated with insulin are successfully switched to sulfonylureas once an HNFIA pathogenic variant is identified.

Glucokinase (GCK)-related MODY (Answer D) is a mild, asymptomatic form of hyperglycemia best characterized by fasting hyperglycemia, but this diagnosis is inconsistent with several features of this case, especially the family history of diabetes-related complications.

5.4. ANSWER: E) Type 1 diabetes (Answer B) can be ruled out by the lack of insulin requirement for up to 8 hours per day, which would only be expected in the first 1 to 2 years after diagnosis.
Congenital reduced pancreatic mass (Answer
C) is associated with pathogenic variants in the HNF1 homeobox B gene (HNF1B) (MODY type 5). This is a rare form of MODY typically accompanied by hepatobiliary and/or urogenital track malformations. Thus, congenital reduced pancreatic mass is unlikely to be the cause of this patient's diabetes. A pathogenic variant in mitochondrial DNA (Answer A) is unlikely given that mitochondrial DNA is exclusively maternally inherited, and this patient's family history of diabetes is consistent with paternal inheritance.

Educational Objective:

Diagnose monogenic diabetes that was initially mischaracterized as type 1 diabetes and assess the treatment implications.

6.1. A 45-year-old ♂ with longstanding T1D underwent a kidney transplant from a living-related donor 2 years ago and is doing well overall. However, despite achieving moderate glycemic control using an automated insulin delivery system without frequent hypoglycemia, he continues to feel that the cost and complexity of his diabetes management regimen cause daily distress. He is interested in a cell-based therapy to treat his diabetes to reduce or eliminate the need for insulin treatment. He is not interested in participating in a clinical trial. Other history includes mild psoriatic arthritis. He does not have coronary artery disease, stroke, or a history of malignancy. He plans to continue working full-time and is physically active.
Lab: HbA1c: 7.4% (4-5.6%) (57 mmol/mol). Cr: 1.6 mg/dL (0.7-1.3). eGFR: 52 mL/min/1.73 m^2 (>60). Tacrolimus 10 ng/mL (trough level, normal 5-15 ng/mL)
Which of the following is the best available option for this patient to consider?

A. Cadaveric pancreatic islet transplantation
B. Encapsulated cadaveric islet cells implanted subcutaneously
C. Stem cell-derived allogeneic islets infused into portal vein
D. Stem cell-derived autologous islets infused into portal vein
E. Whole-organ pancreas transplant

6.2. ANSWER: E) Whole-organ pancreas transplant

Both whole-organ pancreas and islet-cell transplant have been shown to regulate blood glucose levels and reduce microvascular complications associated with type 1 diabetes. Due to the potential risks of immunosuppression, these therapies are typically recommended for individuals with type 1 diabetes who are also undergoing or have previously received a kidney transplant, or for those experiencing recurrent ketoacidosis or severe hypoglycemia despite optimal glycemic control.

The 2021 American Diabetes Association/European Association for the Study of Diabetes consensus report on type 1 diabetes management and the annually updated American Diabetes Association standards of care provide a concise summary of the criteria for β-cell replacement therapy in affected individuals.

6.3. ANSWER: E) Whole-organ pancreas transplant

For overall improvement of quality of life and lifespan of both the kidney graft and individual, whole-organ pancreas transplant after kidney transplant.

(Answer E) is the superior cell-replacement approach in people with otherwise medically uncomplicated type 1 diabetes, especially when adherence to the antirejection regimen is well documented (as indicated by this patient's tacrolimus value in the optimal range).

In 2025, stem cell-derived islet-cell therapy (allogenic and autologous) (Answers C and D) is still investigational and is not available outside of the research environment. This therapy has not been specifically studied in those who have undergone kidney transplant. The first FDA-approved allogeneic cadaveric islet-cell therapy (Answer A), donislecel-jujn, received approval in 2023.

6.4. ANSWER: E) Whole-organ pancreas transplant

However, this therapy is approved for adults with T1D who struggle to maintain Target hemoglobin A levels are elevated due to frequent severe hypoglycemia despite comprehensive diabetes management and education. This therapy may also be considered in individuals whose conditions are too medically complex for whole-organ pancreas transplant, especially after kidney transplant or medical pancreatectomy. This patient does not currently meet established criteria for this therapy. After decades of study, the preferred method of administering cadaveric islets is directly into the portal vein rather than via subcutaneously implanted devices (Answer B). However, this method is being explored for the potential administration of stem cell-derived islets.

Educational Objective:

Describe the current status of the field of HbA1c and islet-cell therapy to treat insulin-deficient diabetes and the therapies that are available for clinical application outside of research environments.

7.1. A 34-year-old pregnant ♀ (G2, P1) with obesity (BMI = 34 kg/m²) and a history of gestational diabetes during her previous pregnancy, presents for preconception counseling. One year ago, she was diagnosed with prediabetes (HbA1c: 6.3% (45 mmol/mol)) and started taking Metformin 500 mg once/day. Since then, she has also increased her physical activity to brisk walking for 45 minutes, 4 days/week and removed refined sugars from her diet. She expresses her desire to become pregnant and wants to optimize her health before conception. Which is the best next step in this patient's management?

A. Continue Metformin at current dosage + add additional day of exercise
B. Stop Metformin and repeat HbA1c measurement in 3 months
C. Stop Metformin and start NPH insulin at bedtime
D. Stop Metformin and start Semaglutide, 0.25 mg weekly
E. Titrate Metformin dosage up to 1500 mg daily

7.2. ANSWER: E) Metformin titrate dosage up to 1500 mg daily

This patient has a history of gestational diabetes, which significantly increases her risk of developing type 2 diabetes. Her current hemoglobin A value (6.3% [45 mmol/mol]) remains in the prediabetes range, and she is on a subtherapeutic dosage of metformin (500 mg daily). Importantly, this degree of dysglycemia in the first trimester predicts macrosomia and should be addressed in the preconception stage whenever possible. The Diabetes Prevention Program trial used metformin, 850 mg twice daily (or an equivalent dose, 1500-2000 mg daily) and demonstrated a 31% reduction in diabetes risk in high-risk individuals, including women with previous gestational diabetes. Increasing the metformin dosage to this level (Answer E) is safe and effective for prediabetes management and aligns with evidence-based strategies for diabetes prevention.

7.3. ANSWER: E) Metformin titrate dosage up to 1500 mg daily

This patient has a history of gestational diabetes, which significantly increases her risk of developing type 2 diabetes. Her current hemoglobin A value (6.3% [45 mmol/mol]) remains in the prediabetes range, and she is on a subtherapeutic dosage of metformin (500 mg daily). Importantly, this degree of dysglycemia in the first trimester predicts macrosomia and should be addressed in the preconception stage whenever possible. The Diabetes Prevention Program trial used metformin, 850 mg twice daily (or an equivalent dose, 1500-2000 mg daily) and demonstrated a 31% reduction in diabetes risk in high-risk individuals, including women with previous gestational diabetes. Increasing the metformin dosage to this level (Answer E) is safe and effective for prediabetes management and aligns with evidence-based strategies for diabetes prevention.

7.3. ANSWER: E) Metformin titrate dosage up to 1500 mg daily

While continuing metformin at the current dosage and adding an additional day of exercise (Answer A) may be reasonable, especially in cases of poor tolerance to higher metformin dosages, exercise's relative effectiveness in delaying diabetes onset in individuals treated with metformin has not been established. Current consensus is that the risk of stopping metformin in the preconception stage in women at high risk of developing overt diabetes is greater than the potential risks of fetal exposure to metformin. Based on numerous retrospective, observational, and small randomized controlled trials, metformin is considered safe in pregnancy, particularly in the first trimester. Simply stopping metformin (Answer B) may lead to higher blood glucose in the first trimester, affecting early fetal development and major organ development, often at a time when a pregnancy is not yet recognized.

7.4. ANSWER: E) Metformin titrate dosage up to 1500 mg daily

Moreover, in women with obesity, as in this case, metformin may be beneficial during pregnancy. In a randomized controlled trial of metformin versus placebo in 400 pregnant women with obesity (but without diabetes), metformin resulted in a 76% lower risk of preeclampsia.

GLP-1 receptor agonists (Answer D) are currently not recommended during pregnancy due to limited safety data and should not be used in women trying to conceive

There is no indication for insulin therapy (Answer C) at this stage, as her glycemic status does not meet diabetes criteria, and insulin would increase the risk of hypoglycemia and weight gain.

Educational Objective:

Guide to preconception counseling in a woman with prediabetes

8.1. A 79-year-old ♂ with T2D is currently undergoing a lumbar laminectomy. You are consulted for postoperative glucose management. He received dexamethasone, 4 mg IV, before induction of anesthesia. His outpatient diabetes regimen consists of Metformin 1000 mg twice/day, and Glimepiride 10 mg/day, last taken the day before surgery

Preoperative lab: Glucose 178 mg/dL (70-99 mg/dL) (SI: 9.9 mmol/L [3.9-5.5 mmol/L]). Cr: 1.2 mg/dL (0.7-1.3). HbA1c: 6.8% (4-5.6%) (51 mmol/mol). Hematocrit: normal

Which is the expected glucose pattern in this patient in the next 72h?

A. Fasting normoglycemia + marked hyperglycemia for 2h following meals
B. Fluctuating glucose with intermittent hyper + hypoglycemia for 48h
C. Persistent hypoglycemia for 24 hours
D. Progressive hyperglycemia peaking within first 24h + resolving over 72h
E. Transient hyperglycemia resolving within 24 hours

8.2. ANSWER: D) Progressive hyperglycemia peaking within the first 24 hours and resolving over 72 hours

This patient received dexamethasone, a corticosteroid that induces insulin resistance, leading to steroid-induced hyperglycemia. The typical glucose response to dexamethasone, 4 mg intravenously, includes onset of hyperglycemia within 6 to 12 hours, peak hyperglycemia within 24 hours, and gradual resolution over 72 hours as steroid effects wane. In hospitalized patients, especially those undergoing surgery, the combined effects of surgical stress, inflammation, and steroids contribute to worsening hyperglycemia, often requiring temporary insulin therapy even in patients who previously had good glycemic control on oral agents. Dexamethasone has a prolonged effect, and hyperglycemia typically peaks in the first 24 hours and does not resolve within 1 day (Answer E).

8.2. ANSWER: D) Similarly, while shorter-acting glucocorticoids, such as daily-dosed prednisone, may produce a classic pattern of isolated postmeal hyperglycemia and normal fasting glucose (Answer A), this is less commonly seen with dexamethasone. Fasting in the setting of prolonged effect of sulfonylurea can lead to hypoglycemia; this is common in individuals with a reduced glomerular filtration rate (<30 mL/min per 1.73 m^2) who were recently exposed to sulfonylurea. However, this patient's glomerular filtration rate is normal, he held glimepiride as instructed on the day of surgery, and the effect of the glucocorticoid would be expected to overpower the potential for fasting-induced hypoglycemia (Answer C), yielding persistent hyperglycemia instead. Glycemic variability (Answer B) is common in the setting of supraphysiologic glucocorticoids, but hypoglycemia is generally seen only during the withdrawal phase of the drug's effect and in the setting of insulin therapy.

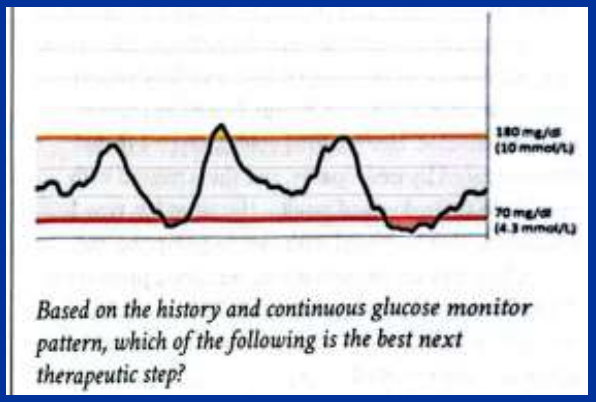
Educational Objective:

Anticipate the effect of perioperative dexamethasone on the glucose pattern in an individual with established diabetes.

9.1. A 30-year-old ♀ with T1D presents at 26 weeks' gestation for diabetes management. She reports experiencing more frequent episodes of hypoglycemia in the last week. Two days ago, about three hours after dinner, she had to ask her husband for help treating a glucose level of 48 mg/dL (2.7 mmol/L) detected by her continuous glucose monitor (validated to be 52 mg/dL [2.9 mmol/L] using a fingerstick). The glucose level corrected to 72 mg/dL (4.0 mmol/L) within 15 minutes of drinking 4 oz of juice. Other than being challenged by a more erratic schedule lately, she feels well and the pregnancy is progressing normally. Her diabetes management includes insulin glargine and mealtime insulin lispro. Two weeks ago, her premeal insulin-to-carbohydrate ratio was intensified from 1 unit to 10 g of carbohydrate to 1 unit to 8 g of carbohydrate in response to frequent episodes of 1- and 2-hour postmeal hyperglycemia. Her continuous glucose monitor output (see image) demonstrates a typical recurrent pattern during the day. 180 mg/(10 mmol/L). 70 mg/(4.3 mmol/L).

9.2. Based on the history and continuous glucose monitor pattern, which is the best next therapeutic step?

A. Change premeal insulin/carbohydrate ratio to 1:12 and continue injecting insulin 15 minutes before the first bite.
B. Continue the 1:8 insulin/carbohydrate ratio but inject insulin 30 minutes before the first bite.
C. Continue the 1:8 insulin/carbohydrate ratio but inject insulin immediately after the first bite
D. Change the premeal insulin/carbohydrate ratio to 1:6 and continue injecting insulin 15 minutes before the first bite.
E. Change the premeal insulin-to-carbohydrate ratio to 1:6 but inject insulin 30 minutes before first bite


180 mg/dl
(10 mmol/L)
70 mg/dl
(4.3 mmol/L)
Based on the history and continuous glucose monitor pattern, which of the following is the best next therapeutic step?

9.3. ANSWER: B) Continue the 1:8 insulin-to-carbohydrate ratio but inject insulin 30 minutes before the first bite

Late second trimester is a typical time for insulin needs to rise during pregnancy in women with pregestational diabetes. Dosage increases must be accompanied by reinforcement of key self-practices to achieve optimal control and prevent hypoglycemia. The continuous glucose monitor pattern shows postmeal hyperglycemia (often ≥180 mg/dL (≥10.0 mmol/L)) followed by low blood glucose and/or hypoglycemia, which she reports validating with concomitant fingerstick measurements. This is a classic pattern indicating that the timing of the prebolus is later than it ideally should be, thereby "missing" the peak effect of carbohydrate absorbed from the gastrointestinal tract and impacting blood glucose at a time when glucose is already declining, leading to hypoglycemia.

9.4. ANSWER: B) This is best addressed by moving the premeal insulin injection earlier, such as 30 minutes before the first bite (thus, Answer B is correct and Answer C is incorrect). This must be advised with an eye toward patient safety, as it may not always be easy for a patient to predict meal timing. Current recommended glucose targets in pregnancy:
Premeal glucose <95 mg/dL (<5.3 mmol/L)
1-hour glucose <140 mg/dL (<7.8 mmol/L)
2-hour glucose <120 mg/dL (<6.7 mmol/L)
>70% of time spent in the pregnancy range (63-140 mg/dL [3.5-7.8 mmol/L]). Given the postmeal elevations, reducing the insulin dose (Answer A) would lead to more hyperglycemia, especially in the late second trimester as insulin needs are typically rising.

9.4. ANSWER: B)

Increasing the insulin dose by moving the carbohydrate ratio from 1:8 to 1:6 (Answers D and E) may not only increase the risk of hypoglycemia but is probably not warranted if the prebolus timing is corrected. Of note, one can see by reviewing her continuous glucose monitor download that she has not yet set the continuous glucose monitor software to targets closer to the currently recommended pregnancy time-in-range. Doing so may help in both achieving and assessing these goals. While not all device software settings allow for this specific target range, she and/or her provider should be able to set a similar target.

Educational Objective:

Explain how to manage unique glucose patterns commonly seen in pregnant women with type 1 diabetes.

10.1. A 44-year-old ♂ is concerned about a rising trend in his HbA1c level given his strong family history of T2D. His current medications are lisinopril and atorvastatin.

Exam: BP: 120/60. BMI: 32. Findings are otherwise unremarkable.

Lab: HbA1c: 6.1% (4-5.6%) (43 mmol/mol). eGFR: 76 mL/min per 1.73 m^2 (>60). LDL: 110 mg/dL (<100). Based on available studies, which of the following is the most effective intervention to avoid the diagnosis of diabetes in this patient for the next 3 years?

A. Discontinue atorvastatin
B. Exercise 150 minutes/week + follow a reduced-calorie diet
C. Start empagliflozin
D. Start metformin
E. Start tirzepatide

10.2. ANSWER: E) Start tirzepatide: This individual has prediabetes based on his hemoglobin A_1 value between 5.7% and 6.4% (39-46 mmol/mol). In addition, he has obesity (BMI greater than 29.9 kg/m^2). In a recent phase 3, double-blind, randomized controlled trial, 1032 individuals with both obesity and prediabetes received either once-weekly tirzepatide or placebo for 176 weeks, followed by a 17-week off-treatment period. At 176 weeks and 193 weeks, the differences in incidence of new-onset diabetes between treatment and control groups were 1.3% and 2.4% vs. 13.3% and 13.7%, respectively. Representing a greater than 90% reduction in cumulative diabetes incidence with tirzepatide versus placebo. By comparison, in the landmark Diabetes Prevention Program trial, after an average follow-up of 3 years, the differences in incidence of new-onset diabetes between intensive lifestyle intervention, metformin (1500 mg daily), and placebo were 14%, 22%, and 29%, respectively.

10.3. ANSWER: E) Start tirzepatide: The investigators reported that intensive lifestyle and metformin interventions reduced the cumulative incidence of diabetes by 58% and 31%, respectively The tirzepatide prediabetes randomized controlled trial indicates higher potency than previously studied interventions (including lifestyle [Answer B], metformin [Answer DJ], and pioglitazone) for the prevention of type 2 diabetes over 3 years (thus, Answer E is correct). While it is not possible to state with absolute certainty that tirzepatide would be more effective without a head-to-head trial, the tirzepatide study was specific to individuals with obesity, which this patient has. It is important to note that in the tirzepatide study, each group received lifestyle intervention, including counseling sessions focused on healthy meals, a 500-kcal deficit per day, and at least 150 minutes of physical activity per week.

10.4. ANSWER: E) Start tirzepatide: This may explain why the incidence of diabetes in the placebo arm was similar to that in the intervention arm of the Diabetes Prevention Program. Treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitors, or statins, has been associated with an increased incidence of T2D. However, stopping the statin (Answer A) for the purpose of avoiding the transition from prediabetes to overt diabetes is problematic for two reasons: (1) there are no data to support that stopping a statin can delay the onset of T2D, and (2) stopping a statin would significantly reduce the cardiopreventive effect of its medication regimen, which is overall counterproductive since the goal of preventing diabetes is, in large part, to prevent cardiovascular disease.

There are no studies on empagliflozin (Answer C) with respect to diabetes prevention

Educational Objective:

Identify the most effective treatments to prevent progression to type 2 diabetes in people with obesity and prediabetes.

11.1. A colleague in primary care calls with a question about the diagnosis of diabetes. She screened a 44-year-old ♂ who has a grandmother and sister with diabetes. Neither of his parents has diabetes. BMI 28. Because the patient has sickle-cell disease, HbA1c was not measured. Instead, a 75-g OGTT was performed, and the following results: Fasting glucose 116 mg/dL. 1h glucose = 224 mg/dL. 2h glucose = 188 mg/dL. Based on these results, which of the following should be recommended now?

A. Another measurement of fasting glucose to rule out T2D
B. Another oral glucose tolerance test with measurements of serum insulin to assess insulin resistance
C. Genetic testing for pathogenic variants known to cause maturity-onset diabetes in young people
D. Initiation of metformin to treat early T2D
E. Weight loss and exercise to prevent T2D

11.3. ANSWER: E) Weight loss and exercise to prevent type 2 diabetes

The diagnostic abnormalities documented by oral glucose tolerance testing in this patient are impaired fasting glucose and impaired glucose tolerance, both indicative of prediabetes. Therefore, weight loss and exercise should be recommended to prevent type 2 diabetes (Answer E). He does not have diabetes because the fasting glucose concentration is less than 126 mg/dL (<7.0 mmol/L), and the 2-hour value from the oral glucose tolerance test is less than 200 mg/dL (<11.1 mmol/L). The 1-hour value is elevated, but this can occur in persons with prediabetes, and it is not a standard parameter for the diagnosis of diabetes. Diagnosis of diabetes based on fasting glucose requires two separate abnormal values, but repeating this measurement (Answer A) in a patient such as this one who has a non-diagnostic level is not indicated.

11.4. ANSWER: E) Weight loss and exercise to prevent type 2 diabetes

Thus, initiating metformin (Answer D) is incorrect because the patient does not have diabetes. Common forms of maturity-onset diabetes of the young (MODY) are associated with autosomal dominant inheritance, and the presented family history (with neither parent being affected) is not consistent with this diagnosis. MODY is also rare. Thus, genetic testing (Answer C) is incorrect. Although insulin resistance can be inferred from measurement of insulin during an oral glucose tolerance test (Answer B), this is not likely to affect this patient's management.

Educational Objective:

Diagnose prediabetes based on results from oral glucose tolerance testing.

12.1. A ♀ with T2D who lives in Miami, Florida, traveled to Colorado to hike Mount Evans. She experienced problems maintaining her usual excellent diabetes control. She documented consistently higher glucose levels not explained by food or activity. Which factor(s) can affect the accuracy of some blood glucose meter readings?

A. Temperature and altitude
B. Altitude, but not temperature
C. Temperature, but not altitude
D. Neither temperature nor altitude
E. Low barometric pressure weather events

12.2. ANSWER: A) Temperature and altitude

Several physical factors appear to influence the accuracy of blood glucose strips; the most common are altitude and temperature (thus, Answer A is correct and Answers B, C, and D are incorrect).

A group of mountain climbers tested blood glucose systems at 13,500 ft (4,100 m). Glucose oxidase meters overestimated the glucose concentration by 6% to 15%. In another study, glucose oxidase meters overestimated values at low PoE levels and underestimated glucose values at high PoE levels. Glucose dehydrogenase-based systems are oxygen insensitive and are therefore not affected by altitude. A similar observational study was performed comparing continuous glucose monitor accuracy at greater than 10,000 feet and found problems with accuracy at higher altitudes.

12.3. ANSWER: A) Temperature and altitude

However, most modern meters report accuracy up to 8,000 to 10,000 feet, and as high as 13,800 feet for one continuous glucose monitor system. Since Mount Evans is greater than 14,000 feet at its summit, it is not surprising she had difficulty The effect of temperature is less predictable, and it can be either positive or negative at extreme cold temperatures. Temperature can indirectly affect readings by influencing circulation to the skin (cold temperature), which may particularly affect the results of alternate-site testing.

There is no evidence that low barometric pressure (e.g., a rainy day) (Answer E) affects the accuracy of glucose meter readings.

Educational Objective:

Identify environmental factors that can affect the accuracy of some blood glucose meter readings.

13.1. A ♀ with HIV was diagnosed with T2D 17 years ago. Her condition is now managed with insulin alone. She has proliferative retinopathy and stage 3 chronic kidney disease. Her glycemic control has been variable for the last few years, with HbA1c ranging from 5-9.9% (31 to 85 mmol/mol). Recent HbA1c 8.4% (68 mmol/mol). She and her husband are wondering whether her HbA1c is accurate because it varies so widely and does not appear to be consistent with her fingerstick glucose values (in recent months, fasting values were 180-230 mg/dL (10.0-12.8 mmol/L) and pre-diagnosed values were 220-250 mg/dL (12.2-13.9 mmol/L)). She has declined continuous glucose monitoring, both diagnostic and personal, due to extreme skin sensitivity to adhesives. Despite the recent hyperglycemia, she feels
Lab: Cr 1.5 mg/dL (0.6-1.1). eGFR 46 mL/min/1.73 m^2 (>60). HIV viral load 684 copies of HIV per ml. Hb: normal. Ht: normal. Tg: 374 mg/dL (<150). Fructosamine 402 µmol/L (200-285). (correlates with HbA1x, value of 10% 86 mmol/mol)
Which is the most likely underlying condition that explains this patient's HbA1c?

A. Chronic kidney disease
B. Hereditary spherocytosis
C. HIV
D. Hypertriglyceridemia

13.2. ANSWER: B) Hereditary spherocytosis

Because of hemoglobin A_1's integral role in the diagnosis and treatment of diabetes, it is important to recognize clinical scenarios and interfering factors that yield discordant results (i.e., when the hemoglobin A level fails to reflect the mean blood glucose value). Hereditary spherocytosis (Answer B) has been documented as a cause of discrepancy between hemoglobin A_1 and glycemic control in patients with diabetes. This patient currently has a discordantly low hemoglobin A value, despite normal hemoglobin and hematocrit. It has varied over the years without apparent explanation based on fasting blood glucose levels. Given the relatively high frequency of mild hereditary spherocytosis, Early testing should be considered in patients with an apparent discrepancy between hemoglobin Ate and glucose meter readings, even in the absence of anemia.

13.3. ANSWER: B) Hereditary spherocytosis

Alternative glycemic markers are necessary to monitor glycemic control in patients with hereditary spherocytosis. After referral to a hematologist and confirmation of hereditary spherocytosis, continuous glucose monitoring was recommended for ongoing management in view of her labile blood glucose values and the unreliability of hemoglobin A levels. HIV (Answer C) does not, independently, cause hemoglobin A_1 discordance. However, hemolytic anemia can be seen in individuals with HIV, either as an adverse effect of antiretroviral therapy or due to autoimmune hemolytic anemia. In either case, one would not expect a normal hematocrit and/or hemoglobin, as it would not be expected to be transient as with spherocytosis.

13.4. ANSWER: B) Hereditary spherocytosis

In advanced HIV (AIDS), some infections can cause hemolysis, but as the viral load is considered low in this clinical vignette (<1000 copies) and the patient is otherwise well, this would not fit the presentation.

Uremia and marked hypertriglyceridemia (Answer D) (usually concentrations >1750 mg/dL) [>19.78 mmol/L]) may also elevate HbA1c and cause marked discordance between blood glucose (or the glucose management indicator reported by continuous glucose monitoring) and HbA1c. However, this patient has chronic kidney disease without uremia (Answer A) and her triglycerides are only moderately elevated, most likely due to her uncontrolled diabetes. Chronic kidney disease can lead to discordance, but only by, on average, 0.5% HbA1c.

Educational Objective:

Identify hereditary spherocytosis as a cause of discordant hemoglobin A_1 results (i.e., when the hemoglobin A level fails to accurately reflect the average blood glucose level).

14.1. A 65-year-old ♂ presents for evaluation 3 months after hospitalization for diabetic ketoacidosis. He has a 5-year history of T2D. He also has dyslipidemia, hypertension, polymyalgia rheumatica, and was recently diagnosed with metastatic melanoma. His diabetes has been well controlled on Metformin, 2000 mg daily, and Empagliflozin 25 mg/day, with HbA1c: between 6.5-7.2% (48-55 mmol/mol). His eGFR 68 mL/min/1.73 m^2. Other medications: Atorvastatin 40 mg/day, and Ramipril 10 mg/day. Prednisone 10 mg/day, was added 3 months ago to treat polymyalgia rheumatica. BMI between 26-28. His oncologist decides to start Nivolumab and Ipilimumab. He tolerates these drugs without adverse effects. Two months later, he is admitted to the hospital with diabetic ketoacidosis.
Lab: Glucose: 265 mg/dL. Serum β-hydroxybutyrate: 12 mmol/L (<3 mmol/L). HbA1c 7.6% (4-5.6%) (60 mmol/mol). Serum glutamic acid decarboxylase 65 antibodies, negative. After hydration and IV insulin, he recovers and is discharged on a basal and mealtime insulin regimen, in addition to Atorvastatin and ramipril. He returns for follow-up in the outpatient setting 1 week later. Which of the following is the best next step?

A. Add metformin, add Glimepiride, and stop mealtime insulin
B. Continue insulin indefinitely
C. Restart metformin, add Dulaglutide, add Repaglinide + stop mealtime insulin
D. Restart Metformin, add once-weekly Semaglutide + wean him off insulin over the next weeks to months
E. Restart Metformin + Empagliflozin + wean him off insulin over the next weeks to months

14.2. ANSWER: B) Continue insulin indefinitely

This patient has immunotherapy-induced type 1 diabetes, consistent with the timing of initiating nivolumab and ipilimumab, the severity of diabetic ketoacidosis, and coexistent recent-onset primary hypothyroidism (induced by checkpoint inhibitors).

Unleashing the power of the immune system with monoclonal antibodies targeting immune checkpoint receptors has been a major breakthrough, causing a paradigm shift in the treatment of many types of cancer. The deficient antitumor immune response can be restored by blocking inhibitory immune receptors of which cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 receptor (PD-1), and its ligand (PD-L1) have become part of standard-of-care options for many indications, including metastatic melanoma. Immune checkpoint blockade is associated with a unique risk for immune-related adverse effects, affecting the endocrine organs in 4% to 30% of patients.

14.3. ANSWER: B) Continue insulin indefinitely

While hypophysitis and thyroid disorders (in this case, primary hypothyroidism) are the most frequent endocrine immune-related adverse effects, autoimmune diabetes is a rare (1%) but potentially life-threatening effect

The median duration until diabetes onset after the start of immune checkpoint inhibitors is 49 days. The shortest time to onset is 5 days, and the longest time to onset is reported to be 448 days. Remarkably, of patients who develop new-onset type 1 diabetes, 71% do so within 3 months after the first exposure. Most affected patients (76%) present with diabetic ketoacidosis. Almost half of the cases are associated with traditional type 1 diabetes antibodies, most commonly glutamic acid decarboxylase 65 antibodies (as opposed to classic type 1 diabetes, where 70% to 90% of patients have those antibodies).

14.4. ANSWER: B) Continue insulin indefinitely

All affected patients are insulin-deficient at presentation and require permanent treatment with exogenous insulin (Answer B) due to the almost complete destruction of pancreatic cells by immunotherapy Prednisone in this case had no effect on the patient's glycemic control or the diabetic ketoacidosis itself, as his hemoglobin A level was at goal on a prednisone dosage of 10 mg daily. Stopping it would not significantly affect his glycemic control or his insulin regimen. Empagliflozin, along with all other SGLT-2 inhibitors, has been linked to euglycemic diabetic ketoacidosis in type 2 diabetes, often precipitated by an illness, infection, severe dehydration, etc. In this case, there was no precipitating factor and the diabetic ketoacidosis was not euglycemic. Basal and mealtime insulins cannot be stopped or weaned (therefore, Answers A, C, D, and E are incorrect).

Educational Objective:

Diagnose and manage immunotherapy-induced type 1 diabetes.

15.1. A 26-year-old ♂ with a 5-year history of T1D is referred because he is interested in an automated insulin delivery pump. He travels often for work and has an erratic eating schedule. However, he has good glycemic control and no longer wants to administer multiple daily insulin injections. His current insulin regimen consists of insulin glargine, 22 units at bedtime, and insulin lispro, 6 units with each meal (total daily insulin dose: 40 units). He chooses an automated insulin delivery system that dynamically adjusts programmed basal insulin rates every 5 minutes to achieve target glucose levels. Continuous glucose monitoring output is as follows: Time-in-range: 78%. Time-below-range: 5%. Time very low-below-range: 0%. Average glucose = 142 mg/dL. Exam: BMI 24. Exam findings are unremarkable. A recent HbA1c: 6.9% (4-5.6%) (52 mmol/mol). After he receives education (basal-bolus concept, carbohydrate counting, etc), his current injection regimen should be switched to insulin pump therapy (with lispro) with which of the following parameters?

Answer	Basal rate xu/h	Carbohydrate ratio (1U/xg)	Sensitivity factor (1U/xmg/Dl)
A	0.9	20	60
B	0.6	15	56
C	1.2	15	45
D	1.4	10	36
E	0.6	10	25

15.2. ANSWER: B) Basal rate 0.6 units/h; 15 carbohydrate ratio units/15g; sensitivity factor 1 unit/55 mg/dL

Most automated insulin delivery pumps require accurate pump programming, including the settings used in traditional pumps, such as basal rates, insulin-to-carbohydrate ratio, and sensitivity or correction factor. While recommended approaches vary slightly, a common approach advises estimating the pump total daily dose (TDD) as 0.75 to 1 multiplied by the prepump TDD depending on the patient's glycemic control (with better control leaning toward a lower TDD in this range). The basal requirement is 50% of the TDD, divided by 24 to identify the hourly basal rate. The carbohydrate ratio is typically calculated as 450 to 500 divided by the TDD, and the insulin sensitivity factor as 1700 to 1800 divided by the TDD.

15.3. ANSWER: B) Basal rate 0.6 units/h; 15 carbohydrate ratio units/15g; sensitivity factor 1 unit/55 mg/dL

Answer B approximates optimal parameters as follows:

Prepump TDD-40 40 (0.75) 30 units

30/215 units (basal insulin requirement)

450/3015 for the insulin to carbohydrate ratio

1800/3056 for sensitivity factor

Importantly, while the accuracy of initial programming of automated insulin delivery pump systems is key for initial benefit and safety, the ultimate success of the patient depends more on how well (and, in most cases, how often) they interact with the pump.

Educational Objective:

Convert a regimen of multiple daily insulin injections to insulin pump therapy in a patient with type 1 diabetes.

16.1. A 65-year-old ♂ with T2D complicated by retinopathy is referred by his primary care physician to improve glycemic control in preparation for elective surgery scheduled in 6 weeks. Last year, he achieved his best HbA1c in 2 years (7.8% (62 mmol/mol)) with diet, exercise, and three agents (Metformin, 1000 mg twice/day; Tirzepatide 15 mg once/week; and Empagliflozin 25 mg/day). 4 months ago, he was advised to discontinue Tirzepatide after developing severe pancreatitis unrelated to gallbladder disease.

In addition to the metformin and Empagliflozin, he requires Degludec 220 U/day and insulin Lispro 80 U before meals, 3 times/day. Unfortunately, on this regimen, the glucose management indicator on his continuous glucose monitoring system has been over 9%. He reports that injections are uncomfortable and he is frustrated about the insulin's lack of effectiveness. Exam: BP: 130/79. BMI 42 (increased from 38 kg/m² 4 months ago).

Lab: HbA1c: 9.8% (4-5.6%) (84 mmol/mol). eGFR: 68 mL/min/1.73 m² (>60). Cortisol (8 AM) (after 1 mg dexamethasone): 1.9 µg/dL. Which of the following is the best next step to improve this patient's glycemic control?

A. Add mifepristone to the current regimen
B. Add pioglitazone to the current regimen
C. Continue the same dosage of insulin degludec and switch from insulin lispro 3 times daily to regular U500 insulin, 15 units once daily before breakfast
D. Convert multiple daily injections to continuous subcutaneous insulin infusion therapy with insulin lispro programmed with the current total daily insulin dose
E. Discontinue insulin degludec and lispro and switch to regular U500 insulin 3 times daily

16.2. ANSWER: E) Discontinue insulins 16-degludec and lispro and switch to regular U500 insulin 3 times daily

For individuals with T2D, suboptimal glycemic control, and significant insulin resistance and/or high insulin requirement, the addition of a GLP-1 receptor agonist or a dual GLP-1/GIP agonist is the preferred strategy. However, GLP-1 receptor agonist therapy is contraindicated in those with recent unexplained pancreatitis, particularly if the episode occurred while taking one of these agents. In this case, and especially when glycemic control must be achieved in a short timeframe for elective surgery, insulin is the preferred therapeutic option. However, in patients requiring > 200-300 units of insulin daily, the volume of insulin becomes a problem, both in terms of patient comfort and pharmacokinetics. Large-volume insulin injections are not absorbed predictably. In these cases, U500 insulin should be considered.

16.3. ANSWER: E) Although the formulation of U500 is similar to that of regular insulin, the duration of action is up to 13-24 hours, permitting adequate delivery with 2 or 3 injections per day without a second long-acting insulin (Answer E). Continuing the same dosage of insulin degludec and switching 3 times daily insulin lispro to regular U500 insulin, 15 U once daily before breakfast (Answer C), may be a useful, albeit atypical, strategy in some cases. However, the total daily insulin dose would be significantly reduced and glycemic control
would likely worsen. Recommendations for the conversion from U100 to U500 insulin generally incorporate the baseline U100 insulin doses, as well as the HbA1c level, to determine appropriate doses of concentrated insulin. One randomized titration-to-target trial provided a clear and specific recommendation on how to convert from U100 to U500 insulin to dose either 2-3 times daily: If hemoglobin A is >8.0% (64 mmol/mol) at the time of conversion, use 100% of the U100 insulin total dose.

16.4. ANSWER: E) If HbA1c is ≥ 8% (64 mmol/mol) at the time of conversion, use 80% of the U100 insulin total dose.

Switching to insulin pump therapy (Answer D) is not desirable because large volumes of U100 insulin, either by injection or pump, are poorly absorbed and are unlikely to achieve the target hemoglobin A level. Additionally, most insulin pumps carry no more than 300 units (with one carrying up to 480 units), so this individual would have to change the pump site every 1 to 2 days if using U100 insulin. Using U500 insulin in insulin pumps has been shown to be effective, but this was not listed as an option in this vignette.

Adding pioglitazone (Answer B) for additional insulin sensitization is a reasonable consideration, but it takes more than 8 weeks for its full effect to be realized and is therefore not a reliable short-term solution. Mifepristone (Answer A) is not indicated because results from the dexamethasone-suppression test are normal.

Educational Objective:

Treat severe insulin resistance with U-500 insulin.

17.1. A 66-year-old ♀ is referred for management of T2D. She has been treated with metformin for 6 years, and an SGLT-2 inhibitor was added 1 year ago. She has dyslipidemia, hypertension, and chronic kidney disease. Her medications are dapagliflozin, Metformin, rosuvastatin, amlodipine, carvedilol, and lisinopril. After 2 attempts and despite slow titration, she is unable to tolerate GLP-1 receptor agonist treatment.

Exam: BP: is 138/84. BMI: 29.

Lab: HbA1c: 7.4% (4-5.6%) (57 mmol/mol). eGFR: 53 mL/min/1.73 m^2 (>60). If Linagliptin is added to the patient's regimen, it will target which of the following pathogenic defects?

A. Hepatic glucose output and β-cell dysfunction
B. Hepatic glucose output and satiety
C. Insulin resistance and β-cell dysfunction
D. Glucagon secretion and insulin resistance
E. Renal glucose reabsorption and satiety

17.2. ANSWER: A) Hepatic glucose output and β-cell dysfunction

GLP-1 is deficient in persons with T2D. GLP-1 is an incretin produced from the proglucagon gene in the L cells of the small intestine and is secreted in response to nutrients. DPP-4 inhibitors are a class of oral diabetes drugs that inhibit the enzyme DPP-4. This is a ubiquitous enzyme expressed on the surface of most cell types that deactivates GLP-1; therefore, its inhibition could potentially affect glucose regulation through multiple effects. Incretin-based therapies include DPP-4 inhibitors and GLP-1 receptor agonists. DPP-4 inhibitors, by increasing endogenous GLP-1, can stimulate glucose-dependent insulin secretion from the glomerular plexus cells and lower glucagon secretion, thereby lowering hepatic glucose output (Answer A). GLP-1 RA exert the same effects and, in addition, slow gastric emptying and decrease food intake. DPP-4 inhibitors have no effect on insulin action (Answers C and D) or satiety (Answers B and E).

Educational Objective: Summarize the pathogenesis of T2D and the mechanism of action of incretin therapies.

18.1. A 52-year-old ♂ returns for a second 18 opinions regarding his diabetes care. During treatment for a gout flare 4 years ago, he was noted to have an asymptomatic random blood glucose 231 mg/dL. Metformin was prescribed in combination with lifestyle modifications, HbA1c: subsequently decreased from 8.6% to 6.8% (70 to 51 mmol/mol). Two years ago, he lost his health insurance, and although he has continued taking Metformin 1000 mg twice/day, he has not seen a physician. Upon obtaining new insurance, he recently returned to his primary care physician, who noted a HbA1c: 9.3% (78 mmol/mol). His medical history is notable for hypertension, seasonal allergies, and recurrent gout, which runs in his family The primary care physician documented normal electrolytes, an eGFR 92 mL/min/1.73 m^2, and normal findings on retinal imaging. However, there is a newly elevated alb/Cr ratio of 148 mg/g Cr (<30).

Exam: BP: 126/78. BMI: 28. There is no evidence of peripheral neuropathy.

His primary care physician prescribed Empagliflozin, but the copay is much higher than he expected. He is wondering whether this is a good choice for him.

Besides cost, which the biggest concern with the use of empagliflozin in this patient?

A. Increased risk for acute kidney injury
B. Increased risk for amputation
C. Increased risk for ketoacidosis
D. Increased risk for severe gout flares
E. Insufficient potency

18.2. ANSWER: E) Insufficient potency.

This patient has established type 2 diabetes and has had loss of glycemic control with monotherapy, as is expected in most classic cases. She is also relatively young, generally healthy, and has early evidence of diabetes end-organ complications, specifically nephropathy A reasonable treatment goal is a hemoglobin A1c value of 7.0% (<53 mmol/mol) or lower if achievable without a significant treatment burden or hypoglycemia. While empagliflozin is a good option for her given the possible albuminuria (which requires a repeat assessment to confirm the diagnosis of nephropathy or stage 1 chronic kidney disease), it is unlikely to lower her hemoglobin A1c by more than 1%, which she requires. Thus, counseling her should include options for reducing her out-of-pocket costs, as well as comparing empagliflozin to other, more potent disease-modifying agents (therefore, Answer E is correct).

18.3. ANSWER: E) Insufficient potency.

For example, it is possible that the out-of-pocket cost of the GLP-1 receptor agonist semaglutide is comparable to that of empagliflozin within her prescription plan. In this case, for optimal disease control, including kidney protection, semaglutide would be a better holistic option for her. Disease control, in her case, includes weight management. She is in the overweight BMI category and would benefit from clinically significant weight reduction (at least 3%–5%). She is more likely to achieve that with a GLP-1 receptor agonist, if affordable, than with an SGLT-2 inhibitor.

Although there is some question about the potency of SGLT-2 inhibitors relative to other oral agents, especially in individuals with a reduced estimated glomerular filtration rate, there is little question now regarding their safety and tolerability.

18.4. ANSWER: E) Insufficient potency.

After several large clinical trials, in addition to postmarketing analyses, the risk of developing ketoacidosis (Answer C) or lower-limb amputation (Answer B) is less than 100 events per 1000 patient-years, which is considered low. When comparing outcomes in patients prescribed an SGLT-2 inhibitor versus a DPP-4 inhibitor, acute kidney injury is actually reduced, not increased, across all levels of estimated glomerular filtration rates (thus, Answer A is incorrect).

Interestingly, in a recent study, this drug class was shown to be protective against gout flares (Answer D) and also when compared with DPP-4 inhibitors. There were also no reports of an imbalanced incidence of gout flares across major clinical trials of SGLT-2 inhibitors.

Educational Objective:

Identify insufficient potency as a potential concern with the use of SGLT-2 inhibitors in the treatment of hyperglycemia.

19.1. An 82-year-old ♀ with T2D is referred 26-year history of T2D. With recurrent hypoglycemic events. She has not been able to tolerate metformin, SGLT-2 inhibitors, or GLP-1 receptor agonists. Her current diabetes treatment regimen consists of insulin degludec, 30 units at bedtime; Alogliptin 25 mg/day; and Nateglinide 120 mg before meals. She measures her blood glucose three times daily. Over the past few weeks, she has documented several blood glucose values < 50 mg/dL (<2.8 mmol/L) before and after meals, but she has not felt any symptoms of hypoglycemia. HbA1c: 6.2% (44 mmol/mol). Lab: blood chemistry, urinalysis, and liver function tests are within normal limits. Which is the best next step in this patient's care?

Answer	Insulin Degludec	Nateglinide	Alogliptin
A	Decrease to 20 U/bedtime	Continue	Discontinue
B	Decrease to 20 U/bedtime	discontinue	Continue
C	Replace with 30 U of insulin Detemir	Discontinue	Discontinue
D	Replace with 10 U of twice daily NPH	Discontinue	Continue
E	Discontinue	Discontinue	Discontinue

19.2. ANSWER: B) Decrease insulin discontinue nateglinide; continue alogliptin: Individuals with recurrent treatment-associated hypoglycemia can experience hypoglycemia unawareness or hypoglycemia-associated autonomic failure. Hypoglycemia unawareness is characterized by a reduction in the sympathoadrenal and autonomic responses and is more common in those with longer duration of T2D and in older adults. This syndrome can lead to a prolonged exposure to hypoglycemia, resulting in loss of consciousness, seizures, or brain damage. However, it is possible to improve glycemic control and reduce the frequency of hypoglycemia with short-term relaxation of glycemic targets. This hypoglycemia avoidance includes reducing insulin therapy for several weeks to allow the patient's blood glucose levels to run slightly higher, thereby increasing sensitivity to symptoms. In addition, the glycemic targets in older patients are more relaxed With a HbA1c level, the goal is between 7-8% (53-64 mmol/mol).

19.3. ANSWER: B) Accordingly, this patient's insulin dosage should be decreased by 20% to 30% given recurrent clinically significant hypoglycemia (<55 mg/dL [<3.1 mmol/L]), and insulin secretagogues (e.g., nateglinide, which is a meglitinide) should be discontinued (Answer B). Although approaches that discontinue the insulin secretagogue are preferred, replacing degludec with the same dose of insulin detemir (Answer C) or NPH (Answer D) would not resolve the issue. An approach that continues the use of an insulin secretagogue (Answer A) should be avoided. Alogliptin is a DPP-4 inhibitor that enhances glucose-dependent insulin secretion (as opposed to meglitinides and sulfonylureas) and it does not increase the risk of hypoglycemia. Lastly, after > 20 years of diabetes and with the resulting decline in insulin production, discontinuing all therapy (Answer E) is likely to lead to symptomatic and problematic hyperglycemia.

Educational Objective: Manage hypoglycemia in patients with T2D.

20.1. A 51-year-old ♂ with hypertension, dyslipidemia, and a 2-year history of T2D presents for a follow-up visit. He takes metformin, HbA1c: 6.8% (51 mmol/mol). BMI 38 (weight 120 kg). He reports that he has been adhering to a low-carbohydrate, ketogenic diet and an exercise regimen for the past 3 months. He is excited that he has lost 3.6 kg and feels more energetic. A more detailed review of his diet reveals that he is eating primarily high-protein, high-fat foods derived from animal products To best support sustainable metabolic control, which of the following strategies should be advised?

A. Begin Dapagliflozin and continue current diet and exercise regimen
B. Begin Linagliptin and switch to a calorie-restricted, low-fat diet in addition to current exercise regimen
C. Begin Semaglutide and continue current diet and exercise regimen
D. Continue current diet but increase the frequency and intensity of exercise regimen

20.2. ANSWER: C) Begin semaglutide and continue current exercise regimen

Altering the macronutrient distribution of the diet is a very common strategy for commercial diet plans. Several randomized controlled trials of low-carbohydrate diets address this issue. In persons with obesity, intake of low-carbohydrate, ketogenic diets seems to cause greater weight loss and loss of body fat than calorie-restricted, low-fat diets, at least for periods of 3 to 6 months. In inpatient studies, isocaloric diets lead to the same degree of weight reduction as ketogenic diets, regardless of the proportions of fat and carbohydrate, and there are no major thermogenic advantages to lowering the percentage of carbohydrate and increasing the percentage of fat and protein in the diet Studies in free-living participants have confirmed that diets based on such regimens do not increase the metabolic rate

20.3. ANSWER: C) While diuresis due to increased salt excretion occurs with caloric restriction in general, persons following low-carbohydrate diets lose fat mass comparable to those with equivalent weight loss from other regimens. The best explanation for the short-term effectiveness of low-carbohydrate regimens is that they are more satiating, or that they reduce caloric consumption by limiting food choices.

Based on evidence in the literature, there is no need to recommend that this patient change from his current diet (Answer B). It is important to monitor the usual markers of diabetes management—hemoglobin A1c, blood pressure, and lipids—to ensure that he does not have a response to the low-carbohydrate diet that differs from that of participants in published clinical trials. However, as long as he continues to lose weight, or maintain a reduced body weight, he will most likely have a positive response in clinical parameters.

20.4. ANSWER: C) The key clinical issue is his obesity. Numerous investigations show that one needs to reduce weight by more than 5% (and closer to 10%) to make a significant impact on insulin resistance and maintain durable glycemic control. Perhaps the best evidence to support this includes trials testing various approaches to achieve diabetes remission (typically defined as achieving hemoglobin ATC levels <6.5% [<48 mmol/mol] off medications). He He has lost 3% of his body weight, for which he should be congratulated, but this is suboptimal for long-term benefit. The addition of semaglutide, a GLP-1 receptor agonist, to his treatment regimen (Answer C) would most likely help him succeed and lead to durable metabolic control. Linagliptin (Answer B) would have a mild-to-moderate effect on his glycemic control, but the use of DPP-4 inhibitors is not associated with weight loss.

20.5. ANSWER: C)

It is not clear whether SGLT-2 inhibitors (Answer A) are safe in persons adhering to a ketogenic diet. Regardless, they would not yield adequate or durable weight loss.

Increasing the frequency or intensity of his exercise regimen (Answer D) is unlikely to help him lose additional weight. Exercise has been shown to be key to maintaining weight loss; however, in most cases, it does not cause weight loss, as it is difficult to expend enough calories through exercise to create a net negative daily caloric balance

Educational Objective:

Describe the effectiveness of available options for medical nutrition therapy and pharmacologic treatments in the management of obesity in people with type 2 diabetes.

21.1. A 72-year-old ♀ has a 22-year history of T2D. She also has hypertension and chronic kidney disease. She is referred for suboptimal glycemic control with HbA1c ranging between 8.5% and 10.0% (69-86 mmol/mol). She is taking 40 U of insulin glargine twice daily and 22 U of insulin lispro 3 times/day with meals. She misses one to two of her insulin doses every week. Her other medications are dulaglutide, 3 mg weekly, pravastatin, enalapril, metoprolol, hydrochlorothiazide, pantoprazole, and escitalopram.

Exam: BP: 142/90. BMI: 48. She has a 2/6 systolic ejection murmur and 1+ edema in her lower extremities.

Lab: HbA1c: 9% (4-5.6%) (75 mmol/mol). eGFR: 48 mL/min per/1.73 m^2 (>60). Urinary alb/Cr ratio: 154 mg/g Cr (<30).

Which is the best next step in this patient's glycemic management?

A. Add canagliflozin, 100 mg daily
B. Increase dulaglutide dosage to 4.5 mg weekly
C. Increase each of her insulin doses by 20%
D. Switch dulaglutide to tirzepatide
E. Switch twice-daily insulin glargine U100 to once/day degludec U200

21.2. ANSWER: D) Switch to dulaglutide: Further intensifying insulin therapy (Answer C) is not recommended in individuals whose regimens have not yet been optimized with insulin-sensitizing therapies, including high- or very-high-potency GLP-1 receptor agonist therapy, especially in the setting of obesity. In this case, weight loss would also independently lower hemoglobin A. Per the American Diabetes Association's framework, higher-dosage dulaglutide (3 mg and 4.5 mg) is very high potency for glycemic control but high potency for weight loss, whereas tirzepatide is very high potency for both conditions. Moving from dulaglutide, 3 mg to 4.5 mg weekly (Answer B) would be expected to produce marginal, if any, improvement in BMI or hemoglobin A. Tirzepatide (Answer D) is the most effective incretin agent available for weight loss in people with type 2 diabetes (weight loss of approximately 10%) and glycemic control (decrease in hemoglobin A 2%), the two short-term goals here.

21.3. ANSWER: D) Switch to dulaglutide: Meta-analyses demonstrate cardiovascular safety. While the results from a large cardiovascular outcome trial comparing dulaglutide and tirzepatide are likely to be available by the end of 2025, tirzepatide was found to lower the risk of a composite outcome, including death from cardiovascular causes or worsening heart failure, compared with placebo in individuals with obesity and heart failure. The best next step in this patient's glycemic management is to switch to tirzepatide before additional steps are taken with insulin (Answers C and E). Switching insulin glargine to insulin degludec (Answer E) at the same total daily dose would not lower the patient's hemoglobin A1 to target. In meta-analyses of phase 3 trials, insulin degludec has been shown to yield hemoglobin A1 control equivalent to that of insulin glargine.

21.4. ANSWER: D) Switch to dulaglutide:

SGLT-2 inhibitors, such as canagliflozin (Answer A), while modestly weight-reducing, would not lower her hemoglobin A to the target (reasonably set at 7.0% to 7.5% (53-58 mmol/mol) as tolerated) at an estimated glomerular filtration rate of 48 mL/min per 1.73 m^2, especially as her hemoglobin A level is 9.0% (75 mmol/mol) despite a high insulin dosage and treatment with a GLP-1 receptor agonist.

Educational Objective:

Determine how to use insulin-sparing approaches in individuals with severe insulin resistance in the setting of obesity

22.1. A 62-year-old ♂ with a 10-year. History of T2D presents for a follow-up visit 6 months after an acute myocardial infarction. He had a previous myocardial infarction at age 58. His current medications are Rosuvastatin 40 mg/day; Metoprolol 50 mg/day; Lisinopril 20 mg/day; Metformin 1000 mg/day; insulin Lispro 4 U before each meal; and Glargine 20 U in the morning. He quit smoking cigarettes 5 years ago after a 20-pack-year history. He has been unable to tolerate GLP1 RA or SGLT-2 inhibitors. Exam: BP: 140/90. Pulse: 68. BMI 30. Lab: HbA1c: 6.8% (4-5.6%) (51 mmol/mol). Glucose: 94 mg/dL. Total cholesterol: 189 mg/dL (<200). Tg: 120 mg/dL (<150). LDL: 72 mg/dL (<100). HDL: 40 mg/dL (>60). In addition to increasing Lisinopril to the maximum tolerated dosage to address his BP, which is the best treatment to address his lipid profile?

A. Add bempedoic acid, 180 mg daily
B. Add ezetimibe, 10 mg daily
C. Add icosapent ethyl, 2 g twice daily
D. Continue current therapy
E. Switch rosuvastatin, 40 mg daily, to atorvastatin, 80 mg daily

22.2. ANSWER: B) Add ezetimibe, 10 mg daily: Clinical trials have shown that individuals at very high risk for cardiovascular disease have a significant reduction in further cardiovascular events with an aggressive regimen of high-intensity lipid-lowering therapy. For people with diabetes and atherosclerotic cardiovascular disease (ASCVD), treatment with high-intensity statin therapy is recommended to obtain an LDL-cholesterol reduction of 50% or more from baseline and an LDL-cholesterol goal less than 55 mg/dL (<1.42 mmol/L). If this goal is not achieved on maximum tolerated statin therapy, the addition of either ezetimibe or a PCSK9 inhibitor with proven benefit is recommended. These recommendations are based on the observation that the degree to which LDL cholesterol is lowered is related to the degree of reduction in cardiovascular events in both lower-risk (primary prevention) and high-risk individuals with established cardiovascular disease in randomized trials, as well as the mean achieved LDL-cholesterol value of 55 mg/dL in several trials (e.g., IMPROVE IT and JUPITER), showing superior benefit in the highest-risk individuals.

22.3. ANSWER: B) Add ezetimibe, 10 mg daily: As a result, the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines were the first to reintroduce the combined concept of both intensive LDL-cholesterol lowering and risk-defining LDL targets. Thus, simply continuing current therapy (Answer
D) is not adequate. Ezetimibe (Answer B) is not a high-potency agent for lowering LDL cholesterol, but in combination with statin therapy, it has been shown to reduce cardiovascular events. Importantly, in the IMPROVE IT trial, which tested the effectiveness of this regimen, the average achieved LDL cholesterol concentration was 55 mg/dL (1.42 mmol/L), which is achievable, as his LDL cholesterol concentration is already 72 mg/dL (1.86 mmol/L). This means he only needs approximately a 23% reduction. For persons with diabetes and ASCVD, a high-intensity statin (i.e., atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily) is recommended.

22.4. ANSWER: B) Add ezetimibe, 10 mg daily: As a result, the 2019 European Society Switching between these two agents at maximum dosage (Answer E) is unlikely to reduce his LDL cholesterol concentration lower than his current medication already has Additional risk reduction comes with addressing hypertriglyceridemia, when present, with icosapent ethyl (Answer C). However, because this patient's triglyceride concentration is normal, icosapent ethyl is not indicated. While bempedoic acid (Answer A) is recommended as an alternative to statin therapy, it has not been demonstrated to be beneficial on cardiovascular outcomes when used in combination with statin therapy.

Educational Objective:

Recommend appropriate intensive lipid-lowering therapy in patients with type 2 diabetes and coronary artery disease.

23.1. Diabetes recently diagnosed in a 56-year-old ♀ when she was found to have fasting plasma glucose concentration of 147 mg/dL (8.2 mmol/L) at her annual physical visit. She has no symptoms of hyperglycemia Other abnormal Lab: AST 119 U/L (20-48) (SI: 1.99 µkat/L [0.33-0.80 µkat/L])
ALT 134 U/L (10-40). HbA1c: 6.9% (4-5.6%) (52 mmol/mol
She has no family history of diabetes. Several of her relatives have had liver disease, but she does not know the cause. She has had oligomenorrhea for several years and has not had a period for more than 4 months
Exam: mildly enlarged, nontender liver. There are no ascites or other signs of chronic liver disease, and she does not have pedal edema. Liver US shows a mildly enlarged liver without masses, no evidence of steatosis, and no biliary disease. Hepatitis (A, B, C) serologies are negative.
Which tests is most likely to reveal the etiology of this patient's diabetes?

A. HNFIA genetic testing
B. Mitochondrial antibody titers
C. Serum ceruloplasmin measurement
D. Transferrin saturation
E. Zinc transporter 8 (ZnT8) antibody measurement

23.2. ANSWER: D) Transferrin saturation:

Whenever diabetes is diagnosed, the possibility of secondary diabetes should be considered. Secondary diabetes occurs when a separate condition leads to hyperglycemia These forms of diabetes are considered distinct from typical T1D or T2D, although clinical features are often shared. Broad categories of secondary diabetes include medication-induced (e.g., corticosteroids), other endocrinopathies (e.g., acromegaly), pancreatic diseases (e.g., pancreatitis), infections (e.g., cytomegalovirus), and genetic conditions (e.g., Rabson-Mendenhall syndrome). One relatively common condition that should be considered is hemochromatosis, or iron overload. Primary hemochromatosis is the most common genetic disorder in the United States, affecting approximately 1 in every 200-300 Americans. It is more common in people of Western European descent.

23.3. ANSWER: D) Transferrin saturation:

It results from increased absorption of iron through the gastrointestinal tract, with excess iron deposition in many tissues. Traditional teaching has been that hyperglycemia results from iron deposition in the pancreas, leading to islet-cell dysfunction. However, recent data suggest that the pathogenesis primarily involves insulin resistance with secondary β-cell decompensation, as in routine cases of type 2 diabetes. Secondary hemochromatosis includes conditions characterized by increased red blood cell breakdown or a history of many blood transfusions (thalassemia, sideroblastic anemia, hemolytic anemia). The clues in this case include amenorrhea (due to hypogonadotropic hypogonadism from pituitary iron deposition) and hepatic dysfunction and enlargement.

23.4. ANSWER: D) Transferrin saturation:

The presence of an HNFIA pathogenic variant (Answer A) is diagnostic of maturity-onset diabetes in the young, which does not apply to this case.

Zinc transporter 8 antibodies (Answer E) would be elevated if this were type 1 diabetes or latent autoimmune diabetes in adults, but these diagnoses seem unlikely

Measuring serum ceruloplasmin (Answer C) would not be helpful since Wilson's disease is unlikely in this patient (diabetes does not typically occur in individuals with Wilson's disease).

Mitochondrial antibodies (Answer B) are increased in primary biliary cirrhosis, but this is not associated with diabetes.

Educational Objective:

Diagnose hemochromatosis as a cause of secondary diabetes.

24.1. A 52-year-old ♂ with a 10-year history of T2D is referred for a second opinion. He is currently taking Metformin XR 1000 mg once/day, and Semaglutide 1 mg/week. His self-monitored blood glucose values range 80-120 mg/dL (4.4–6.7 mmol/L) before meals and 120-140 mg/dL (6.7–7.8 mmol/L) 2h after meals. He reports rare episodes of hypoglycemia.

His review of his systems is notable for recent fatigue and worsening "heartburn" that he attributes to semaglutide. Additional medications are aspirin, lisinopril, and atorvastatin. For years, HbA1c 6.5-6.9% (48–52 mmol/mol), but 4 months ago It was 7.8% (62 mmol/mol) and a recent value was 8.2% (66 mmol/mol).

Lab: Hb: 8.9 g/dL (13.8-17.2). Cr: 0.8 mg/dL (0.7-1.3). Liver function: normal. TSH: normal. Urinary alb/Cr ratio 205 mg/g Cr (<30).

Which is the most likely cause of this patient's high hemoglobin A?

A. Albuminuria
B. High nighttime blood glucose levels
C. Hemolysis
D. Iron deficiency
E. Laboratory error

24.2. ANSWER: D) Iron deficiency

Although the international standardization of the hemoglobin A_1e assay has decreased potential technical errors in interpreting results, several biologic and patient-specific factors can cause misleading values HbA1c values are influenced by red blood cell survival. Thus, falsely high values in relation to mean blood glucose values can be obtained when red blood cell turnover is low, resulting in a disproportionate number of older red cells. This problem can occur in patients with iron, vitamin B, or folate deficiency anemia (Answer D). The most common cause of iron deficiency in adults is slow gastrointestinal blood loss. The individual's risk factors include aspirin therapy, which is no longer recommended for primary prevention of atherosclerotic cardiovascular disease due to a small, but significant, increase in bleeding. The next step in his evaluation, after stopping aspirin, is to refer him to gastroenterology for evaluation.

24.3. ANSWER: D) Iron deficiency

In contrast, rapid red blood cell turnover leads to a greater proportion of younger red cells and falsely low hemoglobin A_1e values. Examples include patients with hemolysis (Answer C); patients treated for iron, vitamin B_{12}, or folate deficiency; and patients treated with erythropoietin. Laboratory error (Answer E) is unlikely to happen twice—both of the patient's hemoglobin A1c values were high at 7.8% (62 mmol/mol) and 8.2% (66 mmol/mol).

Albuminuria (Answer A) does not affect hemoglobin A1c. However, severe proteinuria can affect fructosamine measurement.

High nighttime blood glucose values (Answer B) do not typically occur suddenly and without a rise in fasting blood glucose.

Educational Objective:

Diagnose iron deficiency anemia as a cause of falsely high hemoglobin A1c values.

25.1. A 36-year-old ♂ (weight 80 kg) with a 10-year history of T1D was admitted to the hospital 7 days ago with severe DKA in the setting of acute pancreatitis. After receiving intravenous fluids and insulin infusion, his serum ketones and anion gap normalized. However, his amylase and lipase levels are still elevated, and he is unable to tolerate enteral nutrition. Total parenteral nutrition (TPN) is started.
Two days later, his insulin infusion rate is 2 units/hour with blood glucose: 140-180 mg/dL (7.8–10 mmol/L). The medical team decides to stop the IV insulin infusion because of difficult venous access. Which is the best alternative approach to his insulin therapy?

A. Add 40 units of regular insulin to the TPN bag
B. Add 20 U regular insulin to the TPN bag + 20 U/SC Glargine/day.
C. Add 38 U Lispro to the TPN bag + 10 U/SC glargine/day.
D. Start SC regular insulin sliding scale.
E. Start SC insulin Lispro 10 U/q6 hours

25.2. ANSWER: B) Add 20 units of regular insulin to the TPN bag and 20 units of subcutaneous insulin glargine daily.

In patients receiving total parenteral nutrition (TPN), insulin may be administered as part of the nutritional solution, if allowed by the hospital pharmacy To determine the correct insulin dose to add to the TPN fluid, a separate infusion of regular insulin can be used initially. Once blood glucose levels have reached their target, the total daily dose of regular insulin provided by the insulin drip is calculated. In those without insulin-requiring diabetes, up to 80% of this amount can be added to the TPN fluid as regular insulin to be delivered over 24 hours. For example, if the intravenous insulin infusion at a steady state is set at 2 units per hour (or 48 units per day), 80% of this amount (-40 units) can be added to the TPN solution by the pharmacy to be administered throughout the day. The amount of insulin can then be titrated every 1 to 2 days, based on glucose monitoring.

25.3. ANSWER: B)

Since more frequent adjustments are impractical and costly, the concurrent use of rapid- or short-acting insulin as a correction every 6 hours will help to fine-tune blood glucose control.

However, in insulin-requiring diabetes, and especially type 1 diabetes, with the described approach, insulin therapy is completely interrupted whenever TPN is interrupted. It is therefore best practice to administer 40% to 50% of the expected total daily insulin requirement as a daily long-acting insulin injection and the remainder as insulin placed in the TPN bag to be infused along with the nutrition over 24 hours. In this vignette (patient receiving 48 units of regular insulin daily), 80% of this amount would be -40 units. Approximately 20 units of regular insulin can be added to the TPN solution, and 20 units of insulin glargine can be administered as a once-daily injection (Answer B).

25.4. ANSWER: B)

Adding 40 units of regular insulin to the TPN bag (Answer A) is incorrect, as it carries a risk of diabetic ketoacidosis in the event that the TPN is interrupted

Starting subcutaneous regular insulin sliding scale (Answer D) is incorrect because a patient with type 1 diabetes needs daily basal insulin; ketosis can occur if only a sliding scale is used Lispro insulin is not used intravenously (in a TPN bag) (Answer C), and when it is used subcutaneously in a patient with type 1 diabetes without basal insulin, it should be given every 4 hours (not every 6 hours [Answer E]) to avoid low insulin levels that could lead to hyperglycemia and ketosis.

Educational Objective:

Manage insulin and total parenteral nutrition in hospitalized patients with type 1 diabetes.

26.1. A 46-year-old ♂ with a 24-year history of T1D and BMI 33 is asking about possible adjunctive treatments that will improve his blood glycemic control without causing weight gain. He has had reasonable glycemic control, and HbA1c 7.4% (57 mmol/mol) on a basal-bolus insulin program that totals 0.8 U/kg/day. However, he has always struggled with consistent carbohydrate counting and finds identifying effective insulin doses for certain higher-fat/higher-carbohydrate meals nearly impossible. Insulin pump therapy with automated insulin delivery was difficult for him due to both feeling like a robot and keloid formation at the insertion sites. He is ready to simply give up and forget about achieving his target HbA1c < 7% (<53 mmol/mol). His eGFR 76 mL/min/1.73 m^2, and urinary albumin is undetectable. He has no diabetes-related complications.

Which medications is approved by the US FDA to add to this patient's insulin regimen to improve both glycemic control and support weight management?

A. Empagliflozin
B. Metformin
C. Miglitol
D. Pramlintide
E. Semaglutide

26.2. ANSWER: D) Pramlintide: Pramlintide (Answer D), an analogue of the naturally occurring hormone amylin, increases satiety, decreases body weight, slows gastric emptying, and suppresses glucagon secretion in conjunction with insulin in both T1D and T2D. It is associated with a modest degree of weight loss in most individuals. Pramlintide has been found to be effective alongside multiple daily insulin injections, as well as with pump therapy. Pramlintide's use has been limited due to the need for premeal bolusing (in addition to requisite insulin prebolus) and hypoglycemia when insulin doses are not adequately adjusted. Newer, longer-acting formulations of amylin are under evaluation for the treatment of both T1D and T2D.
None of the other listed drugs are FDA-approved for T1D, although they are frequently used off-label. Metformin (Answer B) is generally considered weight neutral or is associated with a mild degree of weight loss.

26.3. ANSWER: D) Pramlintide

It has been shown in some studies to reduce the amount of insulin required, but it has no significant effect on HbA1c levels or cardiovascular outcomes. Metformin is also not FDA-approved for use in T1D because of a relative concern regarding the risk of lactic acidosis. Miglitol (Answer C) and other α-glucosidase inhibitors have been tested in T1D and have some effect on postprandial glucose levels and body weight, but they do not significantly reduce HbA1c values in individuals with T1D. There is some evidence that GLP-1 receptor agonists (Answer E) have beneficial effects on β-islet cell function, but this evidence is mostly in animals. Small studies suggest a potential beneficial effect in humans, but only in settings of recent-onset T1D with residual β-cell function (positive C-peptide).

26.4. ANSWER: D) Pramlintide

After 24 years and with an insulin requirement well over 0.5 units/kg per day, it is not likely that he produces endogenous insulin. As a weight-loss agent alone, semaglutide would be reasonable, but there is no convincing evidence that it improves glycemic control in individuals with T1D. Although SGLT-2 inhibitors (Answer A) may improve glycemic control and cause weight loss, they have not been adequately studied in persons with T1D, nor are they recommended or approved for use in this setting. Also, SGLT-2 inhibitors may increase the risk of diabetic ketoacidosis. Some GLP-1 RAs and SGLT-2is may be selected based on their cardiorenal benefits if the patient has chronic kidney disease or congestive heart failure, etc. However, none of these conditions are present in this vignette.

Educational Objective

Recommend adjunctive treatments for management of T1D.

The End

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